



LEWELLYS FRANKLIN BARKER, M.B., M.D., LL.D.
A leading internist and the outstanding clinical lecturer of North America.

[Frontispiece to Barker Festschrift.]

INTERNATIONAL CLINICS

A QUARTERLY

OF

ILLUSTRATED CLINICAL LECTURES AND
ESPECIALLY PREPARED ORIGINAL ARTICLES

ON

TREATMENT, MEDICINE, SURGERY, NEUROLOGY, PÆDIAT-
RICS, OBSTETRICS, GYNÆCOLOGY, ORTHOPÆDICS,
PATHOLOGY, DERMATOLOGY, OPHTHALMOLOGY,
OTOLOGY, RHINOLOGY, LARYNGOLOGY,
HYGIENE, AND OTHER TOPICS OF INTEREST
TO STUDENTS AND PRACTITIONERS

BY LEADING MEMBERS OF THE MEDICAL PROFESSION
THROUGHOUT THE WORLD

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NEW ORLEANS

NEW ORLEANS

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Lewellys F. Barker Festschrift, in Honor of his Sixty-fourth Birthday, September 16, 1931

FOREWORD

DEAR BARKER:—It seems but yesterday that we first met when you were working under Welch in the Pathological Laboratory and I was "Differentiating Physician." Differentiating Physician! A portentous title for so modest a position! It seems but yesterday; and it is over forty years ago. Think of it!

Those were inspiring days, were they not? The beginnings of a new institution. Osler, Welch, Halsted, Kelly, Councilman, all young men, the oldest in his forty-first year. All of the traditions which have become so dear to us were yet to be made. In the Pathological Laboratory were Welch and Councilman and Flexner and Nuttall and Reed and Williams; in the wards, Osler and Halsted and Kelly and the group of happy and enthusiastic youngsters who surrounded them; and in the dispensary, Brockway and Finney.

Bacteriology was in its youth and serology in its infancy. Halsted was demonstrating the marvels that could be done in surgery through sound pathologic reasoning and an impeccable technic. Haematozoa and Amoebae were fascinating us in the "Chief's" wards. It seemed to us that there had never been such another day of promise.

It was not long before you joined us in the hospital. How well we, who were your companions, remember the way in which you earned the respect and the love of your colleagues, first on the medical staff, then as Fellow in Pathology. The quiet reserve with which you worked, the neatness and thoroughness with which everything to which you put your head and your hand was done, won the admiration of all. We began to realize how thoroughly you saw and

comprehended that which was going on about you; that your hand was in everything. As I jotted down years ago, you played a part in clinic and laboratory, a part which means so much for the success of any institution, the part of the quiet observer who stops by the desk of student or colleague, compliments him perhaps on some interesting point in his work and passes on almost unnoticed. And then the worker goes ahead and dilates and expands on that point, and never quite realizes that some one else discovered it for him, and that had it not been, perhaps, for that little visit, he might have gone on indefinitely without appreciating what he had brought out. You, my dear Barker, were one of those acute, sensitive spirits, quickening and animating the circle in which you moved.

Dear Doctor Hurd was a jealous guardian of the resources of the hospital and was very particular as to who should be allowed to live in the institution; it was not always easy to convince him that a new house officer was necessary. But he was an equally jealous guardian of its true interests, and when the school opened and you joined Mall's staff, the wise Superintendent thought that it would be well to keep you in the hospital. . . . "He has so good an influence, you know, upon the younger men."

As you look back to those days you must remember how the students looked up to you. Do you recall the greeting that they gave you as you sailed for Europe one summer on the little old North German Lloyd steamer? I doubt if you realize the vacancy that was left in the hearts of all your colleagues when you deserted us for Chicago.

When you came back to us as the welcome successor of the dear "Chief" you had been working for five or six years away from very active association with the clinic. With what keen vision you grasped the needs of the growing service! In the establishment of the biologic, physiologic and especially the chemical division of the medical department you made a contribution of incalculable value to the hospital and the University. In addition to your earlier clinical achievement you had acquired a broad basis as an anatomist, as a pathologist and as one especially interested in the neuropsychiatric

side of medicine. It was not long before your industry, your ability and your learning had launched you well upon the distinguished career which has since been yours.

We were a small group who knew you and loved you forty years ago. The boundaries of your reputation are now world-wide.

We were youngsters forty years ago. Now—well, we are no longer young, but it makes us feel young again, those of us who have worked by your side, to join hands with your pupils and friends of later years in the affectionate greeting which we offer you today.

W. B. Thayer.

DOCTOR BARKER: THE MAN AND THE PHYSICIAN

By FIELDING H. GARRISON, M.D. (Col. U. S. A. Retired)

Librarian, Welch Medical Library, Baltimore

IN ATTEMPTING to set down a few words of appreciation of Dr. Lewellys F. Barker, my mind goes back to his very great kindness to a near relative of mine in his last illness, and what the patient had to say about him: "Ah, that is a *real man*, a real physician, the best I have ever had to attend me." During this painful experience, I had occasion to see Doctor Barker in his office, and the impression gained of him at that time was of one who burned the midnight oil unduly, whose ideals of competence in his profession were of that austere kind which demanded no less than complete control of the literature of any medical problem that happened to interest him. This was indeed confirmed by his visits to the Surgeon General's Library, where, like Thayer, McCrae, Emerson and other internists of the Johns Hopkins Faculty, he gave us freely of his knowledge and experience as to knotty points in the classification of such complex subjects as the paralyses, the arthritides, the spinal arthropathies or the gouty and rheumatic disorders. I shall never forget his quizzical expression when, settling down beside two large trays of indexed titles covering diseases of the spinal cord, he put to me the leading question: "What is primary lateral sclerosis?" That question not only illustrates the keen interest which the medical leaders of the time took in the Index Catalogue and the Index Medicus, but it was to me an incentive, a lightning-flash revelation of the fact that no man can keep track of the mazes of modern medicine without constant, unremitting study. Here, too, was a point of divergence between Osler and Barker: Osler lingering fondly over the past and living in the present with the watchword "Take no thought of the morrow"; Barker, like Allbutt, ever thinking forward into the medicine of the future. Another pleasant recollection I have is of Doctor Barker's friendship for our family physician, the late Dr. Philip S. Roy, who, as Doctor Barker once testified at a Washington meeting, sent him some of the most interesting cases he had ever seen of such undecipherable diseases as

pernicious anæmia. Doctor Roy was a rugged Virginian who read much but wrote little, whose attitude toward making himself particularly known was, indeed, one of blank indifference. Yet, albeit unheralded as such in the ordinary annals of medical science, he has always seemed to me one of the most remarkable bedside practitioners this country has had. To see him take command of a sick room and right an upset family in a few minutes was as inspiring as the sight of a noble ship heading for the open sea. A child, for example, bed-ridden for weeks with an apparently incurable malady: a chance social visit of the old doctor, a mere glance at the patient, requested by the parents; a gruff, simple direction going straight to the cause, and the little sufferer well again in a few days. Here we have the intuitive, seemingly mysterious power of observation, fruit of multifarious experience, which characterizes the natural-born bedside physician. And of such is the true kingdom of medicine. Of this kingdom, Doctor Barker has been a distinguished ornament, and one thinks of him in the light of the western novelist's dictum: "Doctors are as conservative as kings." The physician who lacks this poise, this inflexible devotion to the Hippocratic vow, this insight into the real needs of sick people, may sometimes turn out to be a rogue elephant more dangerous to a patient than a Chicago gunman could ever be. A fair example of Barker's conservatism is apparent in his view of the endocrinopathies. He was one of the earliest expounders of the true significance of the endocrines, yet he has never exceeded the speed limit implied in Schiller's verse:

"Es ist der Geist der sich den Körper baut,"

or that of the old English poet:

"For of the soule the bodie forme doth take,
For soule is forme and doth the bodie make."

Were he mathematically inclined, I fancy he would view such concepts as life, mind, the soul, the integration of the organism, not as ordinary polynomial expressions nor even as linear functions, but as complex functions of several variables, in which the time implication is a fourth dimension. Among the medieval logicians, he would have been a Realist rather than a Nominalist, even as he has steadily opposed the fundamental error of democracy: that ability is engen-

dered by standardized diffusion of knowledge, culture and well-being, instead of the other way around. "Much learning," said Heraclitus, "does not make mind." In the medical societies, Barker's keen mind, tempered by his essential Anglo-Saxon conservatism, has played with those perilous matters lightly. His interests have ranged from anatomic teaching and terminology to experimentation upon himself, from complex schemes of diagnostic tests to the ultimate nature of man, but he has always kept his balance true and never lapsed into the pitfalls in wait for the unwary. An austere devotion to duty and the things of the mind is set off by a distinction of appearance, a charm of personality, a hospitable nature, an open-minded freedom from prejudice, an innate kindliness of disposition, which are by no means least among the attributes of the beloved physician. To the medical librarians he has been, like Osler, a constant friend. His devotion to truth and knowledge was an incentive to the serious study of medical literature in our youth. As we approach the Great Divide, we are proud to be still honored by his friendship.

Clinical Presentation of Cases at the Harvard Medical Society*

- (1) TWO CASES OF PROGRESSIVE MUSCULAR WASTING
- (2) A CASE OF LETHARGIC ENCEPHALITIS WITH INVOLVEMENT OF THE BRAIN STEM
- (3) A CASE OF PULMONARY TUBERCULOSIS AND PROFOUND UNDER-NUTRITION, WITH COMMENTS UPON THE INSULIN-FATTENING CURE.

By LEWELLYS F. BARKER, M.D., LL.D.

Baltimore

INTRODUCTION

DOCTOR CHRISTIAN (*Chairman*).—It was a very happy thought, eighteen years ago, when the system of having a "Physician-in-Chief *pro tempore*" was inaugurated. It was an even more happy thought that, at the beginning of that custom, Doctor Thayer should have been invited to serve. Since 1913, we have been favored by a large group of leaders in medicine, and each of them has given us stimulation and new ideas. Our second visiting Physician-in-Chief was Sir Thomas Lewis. He was followed, successively, by Professors Hewlett, Billings, Longcope, Landis, McCrae, Woodyatt, Conner, Herrick, McNider, Lambert, Riesman, Sir H. Rolleston, Duncan Graham, and, last year, McLester, from Birmingham. This year, the seventeenth Physician-in-Chief *pro tempore* has, like the originator, been drawn from Baltimore, and we are glad that Dr. Lewellys F. Barker, of the Johns Hopkins Hospital, has accepted the invitation to come and spend a week with us. I take pleasure in presenting Doctor Barker to the members of the Harvard Medical Society.

DOCTOR BARKER.—I need not say how greatly honored I feel to be named as a member of this group of Physicians-in-Chief *pro tempore*, which Doctor Christian has just mentioned. Mingled with

* Meeting of the Harvard Medical Society in the Amphitheatre of the Peter Bent Brigham Hospital, April 21, 1931.

a feeling of pride, there is, however, when I look over the list of my predecessors, a feeling of humility because of my shortcomings. Still, in medicine, each of us must do the best that he can with the brain-cortex that he has. And there is need for many kinds of cerebral cortices; even a mediocre man can make certain contributions, if he will be but earnest and industrious.

It was one of Doctor Osler's maxims that the way to remain young was to continue "to play with the boys." Hence, in association with the Resident Staff, I look forward to being a "young fellow" again, during the week of work ahead of us; and I am genuinely proud to act as a temporary incumbent of this important office.

TWO CASES OF PROGRESSIVE (CENTRAL) MUSCULAR ATROPHY

Doctor Christian has suggested that I spend an hour, tonight, in demonstrating to you the principal features of three or four cases of unusual clinical interest.

Two of the cases belong to the group of the muscle wastings. Medical students, and even doctors sometimes, seem to have difficulty in placing patients in the several subdivisions of this group. As a matter of fact, the correct assignment to a subdivision is relatively easy, if one but keep in mind a few fundamental principles. The introduction of a long list of names for different syndromes is very confusing to the student when he approaches the study of the muscular wastings. He hears of types named after Aran, Duchenne, Charcot, Tooth, Marie, Déjerine, Erb, Landouzy, Möbius, Hoffmann, Werdnig, Zimmerlin and others, and he finds it very puzzling to keep them all in mind. My plan, tonight, is to outline a few general principles which make the grouping very easy. Let us, however, leave out of consideration, temporarily, one group, the "hypertrophic neural group," and devote our attention to the other forms.

All the rest of these chronic wasting diseases of muscle will be found to fall into two large groups: first, the group of primary muscle wastings; and second, the group of muscle wastings secondary to disease in the central nervous system. The first group, neurologists speak of as the *primary myopathies* or the *muscular dystrophies*, whereas they speak of the second group as the *progressive (central) muscular atrophies*. Of course, the muscle wasting of acute anterior

poliomyelitis is not included, for, though of central origin, it is acute rather than chronic, and it is not progressive.

Between the two great groups mentioned, there are marked contrasts, which I shall now, more or less dogmatically, enumerate.

First, the *age of onset*. In the first group (primary myopathies), we find that it is children or early adolescents who are affected, whereas, in the second group (progressive central muscular atrophies), we do not observe the symptoms and signs until middle life or later.

Secondly, the *distribution of the muscular wasting*. In the first group, or primary myopathies, the muscles of the trunk or of the proximal portions of the extremities are first involved; in the second group, or progressive central muscular atrophies, it is the distal muscles of the extremities that are first affected.

Thirdly, the *presence or absence of fibrillary twitchings*. When definite fibrillary twitchings are observable in association with progressive wasting of the muscles, one can say almost with certainty that the disease is of the progressive central type, that is, it belongs in the second group. This fibrillary twitching is due to irritation of the nerve-cells in the anterior horns of the gray matter in the spinal cord, or in the motor nuclei of origin of the cerebral nerves. Fibrillary twitching is never seen in uncomplicated cases of the primary myopathies.

Fourthly, *familial incidence*. Cases belonging to the first group (primary myopathies or muscular dystrophies) occur in families, whereas in the progressive (central) muscular atrophies, it is usually only one person in a family that is picked out. Heredo-familial incidence, therefore, points to Group I, and its absence to Group II.

Fifthly, the *presence or absence of spastic phenomena*. Spastic phenomena are always absent in uncomplicated cases of Group I. They are sometimes, but not always, present in cases of Group II. The co-existence of hyperreflexia and of positive Babinski reactions with progressive muscular wasting, therefore, points to Group II.

Attention to these five points will make it easy for you to group nearly all the cases of muscular atrophy correctly, except for the hypertrophic neural group that, at the onset, we agreed to leave out of consideration temporarily. I should now like to mention it and its principal features since they are so peculiar that you are not

likely to confuse it with the two great groups discussed. This *hypertrophic neural form*, or so-called "Charcot-Marie-Tooth type" of muscle atrophy, begins most often in the peroneal muscles; we see toedrop, club foot, and "bird's legs." There may seem to be almost nothing but bone left below the knees. The peripheral nerves can be felt to be markedly thickened. When the upper extremities are involved, the atrophy is marked in the forearms. This disease may occur in infancy and tends to be familial.

Now let us study the two patients that have been brought down for differentiation. I shall ask Doctor Diack, the Senior House Physician on the ward in which they are under study, to give you an epitome of the clinical history in each case.

DOCTOR DIACK.—This patient is a sixty-two-year old tailor.

DOCTOR BARKER.—Of course, a dystrophy might have begun in adolescence and the patient could have lived on to be sixty-two.

DOCTOR DIACK.—He came into the hospital complaining of pain in the epigastrium, of seven weeks' duration.

His family history and past history are irrelevant. His *present illness* began about five years ago; he first noticed increasing weakness, most marked in the hands.

DOCTOR BARKER.—This weakness, you will note, was distal, and not proximal, in the extremities.

DOCTOR DIACK.—He had to stop sewing on account of the weakness. In three years his legs had become so involved as to necessitate the use of a cane.

DOCTOR BARKER.—You hear of the slow progression.

DOCTOR DIACK.—Seven weeks ago the patient began to have pain in his epigastrium, which he does not, however, very accurately describe. It seems to be a constant gnawing pain, located in the mid-epigastrium, without radiation, and bearing no relation to food. The patient has never taken soda, so he does not know whether this would relieve him or not. Two weeks ago he began to vomit, but without relieving the pain.

Physical examination, on admission to the hospital, revealed normal eye grounds, except for some arteriosclerotic changes; the pupils reacted sluggishly. There was slight fibrillary twitching and slight but definite atrophy of the right side of the tongue.

DOCTOR BARKER.—The right half of the tongue is smaller than

the left; and there is distinct fibrillary twitching to be seen now, as the tongue is protruded.

DOCTOR DIACK.—The chest, heart, and lungs were negative. The abdomen was obese and flabby and the abdominal reflex was elicited with extreme difficulty.

DOCTOR BARKER.—In an obese elderly person, this is not of much significance.

DOCTOR DIACK.—There was slight tenderness on palpation in the right upper quadrant. The breathing was mostly abdominal and there was a peculiar pulsation in the abdominal wall, apparently synchronous with respiration.

There was wasting of the thenar and hypothenar eminences of both hands. There was fibrillary twitching of the muscles of these groups, almost resembling a tremor.

The triceps reflex was absent on both sides; the biceps reflexes were present, and the radial periosteal reflexes were diminished equally on the two sides. Blood-pressure, 170/100.

Examinations of the lower extremities showed the knee-jerks and ankle-jerks to be present; it was thought that a positive Babinski was obtained at times on both sides, but at other times it could not be elicited.

DOCTOR BARKER.—Suggestive of incipient spasticity, but not yet definite.

DOCTOR DIACK.—Tactile sensation was usually normal, though one observer described impairment of touch.

Laboratory tests were negative, except for a slight leukocytosis (up to 12,000 white blood-cells, and rising to 15,000 after a lumbar puncture). Lumbar puncture revealed normal pressure and dynamics of the cerebrospinal fluid, cells not increased, total protein normal; negative Wassermann and negative gold curves.

Rectal examination revealed a small mass inside the sphincter. A barium enema was done today, which has unofficially been reported as negative. A proctoscopic examination is to be made.

Following the lumbar puncture, he developed a febrile reaction with temperature of 102°. His neck was not stiff, and no cause for the fever could be found. His temperature is now normal again.

DOCTOR BARKER.—The study of the patient is not yet complete, especially with regard to the epigastralgia, the tenderness in the

right upper quadrant, the atherosclerosis and arterial hypertension, and the small mass in the rectum.

We can, however, decide with certainty as to the nature of his muscular wasting. His muscular weakness and atrophy began about five years ago when he was fifty-seven years of age. You will have noted: (1) Onset in mid-life or later; (2) involvement of the distal musculature of the extremities; (3) the presence of fibrillary twitchings; (4) the absence of history of heredo-familial incidence; and (5) the report that a suggestion of spastic phenomena has, at times, been observable. Referring to our list of fundamental criteria, we see that the case falls unquestionably within Group II. As a matter of fact, it is a case of *Aran-Duchenne type of progressive (central) muscular atrophy*, with wasting of the thenar and hypothenar eminences and with development of claw hands. But there are also beginning bulbar symptoms, as shown by the atrophy and fibrillary twitching of half of the tongue. It is not uncommon to have progressive bulbar paralysis associated with the Aran-Duchenne type of progressive atrophy of the extremities.

May I ask Doctor Diack to give us a summary of the history of the second patient?

DOCTOR DIACK.—This next man is a steamboat engineer, forty-two years of age, who entered the hospital complaining of difficulty of speech and of weakness in his right hand.

DOCTOR BARKER.—Please note immediately the co-existence of bulbar symptoms and distal involvement of the muscles of the right upper extremity!

DOCTOR DIACK.—There was no similar disease in his family. His illness probably dates back to one year ago, when he was forty-one. He first noticed the gradual onset of weakness in his right hand. About one month later, he became conscious of weakness in his left hand also. Coincident with this, he noticed that his voice quavered on excitement, and that there was a little slurring of his speech. Six months ago it became difficult for him to make himself understood and his left hand and his legs, which had now become involved, grew progressively weaker. He noticed about two months ago that, when drinking, sometimes a few drops would pass up into his nose.

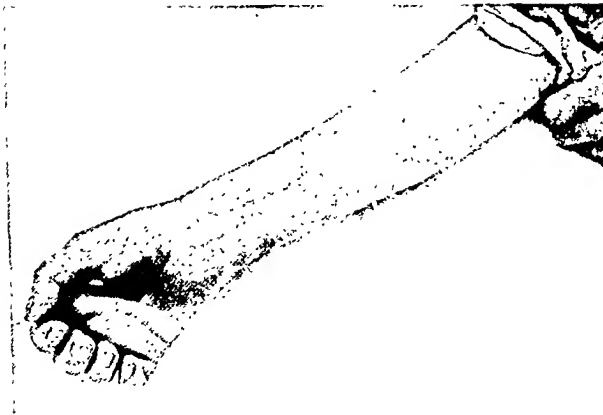
DOCTOR BARKER.—This dysphagia points to involvement of the

FIG. 1.



Claw-hand (palmar view).

FIG. 2.



Claw-hand (lateral view). Note also the marked flattening of the thenar and hypothenar eminences (so-called simian hand).

(Both photographs by Dr. Boyd.)

nucleus ambiguus, the nucleus of origin (in the medulla oblongata) of the motor fibers of the ninth and tenth cerebral nerves.

DOCTOR DIACK.—About two months ago, the loss of strength in his right arm had progressed so that he could no longer extend his fingers.

DOCTOR BARKER.—Look at these hands. We have to deal here with the claw hand or *main en griffe* of the French (Figs. 1 and 2). It is more marked on the right. Notice the marked deepening of the interosseous spaces, due to the muscle wasting.

DOCTOR DIACK.—Physical examination showed that the pupils reacted normally to light and on accommodation and extra-ocular movements were normal, except for slight nystagmus to the right, which was not constant. There is a suggestion of accentuation of the left nasolabial fold, with slight flattening of the right. In the muscles of the trunk there is marked fibrillary twitching; there is atrophy of the muscles of the upper arms and forearms and of the thenar and hypothenar eminences, more on the right. Chest, heart and lungs are negative. In the muscles of the back, a great number of fibrillary twitchings are visible—almost in constant motion. Abdominal examination, negative; leg reflexes, hyperactive; definite positive Babinski on both sides.

DOCTOR BARKER.—The positive Babinski on planter stimulation is characteristic enough to be seen from the back seats of this room. It is more marked on the right than on the left but is positive on both sides. This points indubitably to bilateral pyramidal-tract lesions. A positive Babinski is a part of the spastic phenomena. He tries to let his leg muscles relax, but they are hypertonic and spastic. There is beginning ankle clonus, but it is not well sustained. There is also a suggestion of patellar clonus. All these findings afford definite evidence of pyramidal-tract involvement. You note the slurring of speech when the patient pronounces such words as "truly rural," "episcopal," "separate," and "Massachusetts General Hospital." He exhibits an extreme degree of dysarthria, there is no modulation of his voice, and there is a tendency to scanning. There is, at present, some slight nystagmus to the right, which might make one think of multiple sclerosis, but the patient is forty-one years old and multiple sclerosis starts earlier; moreover, the abdominal reflexes are present, whereas they are practically always absent in multiple

sclerosis. The early signs of multiple sclerosis are (1) Weakness of the abdominal muscles; (2) absence of abdominal reflexes; and (3) bitemporal pallor of the optic discs. The clinical picture in this man is quite different from that of multiple sclerosis.

Here, the onset at the age of forty-one, the beginning of the weakness and of the atrophy in the muscles of the hands, the predominant distal distribution in the extremities, the presence of fibrillary twitching, the absence of familial incidence, and the demonstrability of definite spastic phenomena and of involvement of bulbar domains lead to a diagnosis of *progressive (central) muscular atrophy of the type known as amyotrophic lateral sclerosis*. The patient is also undernourished (thirteen pounds too light), and his hygiene has been faulty.

It would have been just as easy to have shown children with muscular dystrophies (first group) had they happened to be in the hospital. You would, I feel sure, have no trouble in assigning the cases to their proper group. One has simply to remember these five points of contrast that I have emphasized.

LETHARGIC ENCEPHALITIS INVOLVING THE BRAIN-STEM

DOCTOR BARKER.—The next case is of entirely different nature. Will Doctor Diack kindly summarize his history?

DOCTOR DIACK.—This eighteen-year-old schoolboy entered the hospital complaining of "staggering gait and of difficulty of speech and of swallowing."

His *past history* and *family history* are negative. The boy has been exceptionally bright in school, graduating from high school at the top of his class.

The *present illness* dates back about two years. He first noticed "watering of the left eye." He consulted a doctor, who found also paralysis of the left side of the face—there was no expression on that side at all. At this time, the boy showed also a slight hesitancy in his speech, but he continued in school. Six months ago, his right eye began to water and he became paralyzed on the right side of his face. At this time, he noticed a slight return of motion on the left side. He is now troubled by the lachrymation, is unable to close his eyes and his speech defect has become more pronounced. For the past two

months, he has noticed some weakness in his legs and his gait has become staggering. For the past few weeks, when eating, he has had a tendency to regurgitate through his nose; during this time he has also noticed some palpitation of the heart and has suffered a loss of about fifteen pounds in weight.

Physical examination showed pupils that reacted to light and on accommodation. The fundi looked normal. He was unable to move the eyes laterally, nor could he close his eyes completely. He was unable to wrinkle the forehead, although very slight motion occurred on the left side. The jaw (with the mouth open) deviated slightly to the right and, on showing the teeth, the left angle of the mouth was pulled up. The tongue deviated to the right; the palate was normal, except that there was no gag reflex. Laryngoscopic examination showed the larynx seemingly tipped to the right; the vocal cords moved equally and well.

The heart was normal except for tachycardia. Blood-pressure has been as high as 160/105 but usually it is about 140/85. Reflexes are apparently normal, except that the abdominal reflexes are sluggish. There is no weakness of the abdominal muscles. Babinski is negative on both sides. There is definite staggering on walking, but not constantly toward either side. The Romberg test was not definitely positive, although he swayed somewhat.

Laboratory Tests.—He has had a slight but constant leukocytosis (with 79 per cent. polymorphonuclears). The urine and stools have been negative. Lumbar puncture showed fluid under normal pressure with normal dynamics, cell count of 16 (ten polymorphonuclears and six small mononuclears). Wassermann and colloidal gold tests were both negative. A lumbar puncture at the Massachusetts General Hospital before admission here had yielded the same findings, except that only four lymphocytes were found and no polymorphonuclear cells were seen.

DOCTOR BARKER.—When making a diagnostic survey of a neurologic case, it is wise to divide the study into three stages: (1) The accumulation of factual data bearing upon the case (history, physical examination, laboratory tests, *etc.*); (2) consideration of these facts for the purpose, in cases of organic disease, of localizing the site of the lesions; and (3) reflection upon the nature of the malady, its etiology, and its pathogenesis.

The functions of the different parts of the nervous system of this young man have been systematically tested in the ward. The sense of smell (N. I) and the sense of vision (N. II) are normal in this patient. When we get to the oculomotor nerve (N. III), however, we find disturbances. It is true that he can look up, as you see; the M. superior rectus is acting and the M. levator of the upper lid is also acting. But he cannot look downward and he cannot look medial-ward adequately. The medial rectus muscle of the left eye is weak, though the medial rectus muscle of the right eye is still fairly strong. The left third nerve is obviously more affected than the right. The intrinsic muscles of the eye have not been involved, since the pupils contract to light and on accommodation.

On testing the N. patheticus (N. IV) we find that, though he can look upward, he cannot look up and to the side. The eye-position of pathos cannot be assumed.

The trigeminal nerve (N. V) on the right is involved, for he can shove his jaw to the right but not to the left; he has, however, no difficulty in chewing.

The abducens nerve (N. VI) is not functioning, for he cannot turn either eye outward.

The facial nerve (N. VII) is involved on both sides; he cannot wrinkle the right side of his forehead at all, and he wrinkles the left side only slightly. In attempting to show his teeth, he exhibits complete facial paralysis on the right and severe involvement on the left. There is almost complete bilateral seventh nerve paralysis.

The acoustic nerve (N. VIII) is not affected, for he can hear well and there is no history of labyrinthine vertigo.

We know that the glossopharyngeal and vagal nerves (NN. IX and X) have been involved, for you have heard of his dysphagia. At present, the palate is normal, except for absence of the gag reflex.

The trapezius and sterno-mastoid muscles are active, so the spinal accessory nerve (N. XI) is normal.

The hypoglossal nerve (N. XII) is apparently not affected on the left, but may be slightly involved on the right, since the tongue has deviated somewhat to the right when protruded. The larynx is normal intrinsically, but there is some displacement.

In addition, he has shown a little incoördination, tending on walking to fall to one side or the other. There has also been a sug-

gestion of an intention tremor, more on the left than on the right (on finger-nose test). When he walks, instead of swinging the arms naturally, the right arm does not swing; this is a loss of what is known as an "associated movement." So much for the factual data that have been accumulated.

Let us turn to the second phase of the diagnostic inquiry and try to evaluate these data for the localization of the lesions. In the first place, the loss of the associated movement of the arm on walking points to a lesion of the globus pallidus, or of the substantia nigra. The nuclei of the third and fourth cerebral nerves are evidently involved in the floor of the Aqueduct of Sylvius in the midbrain. The symptoms referable to the fifth, sixth and seventh cerebral nerves must be due to injury of the gray matter of the pons, and the involvement of the motor nuclei of the ninth, tenth and twelfth nerves points to lesions in the medulla oblongata. There are no signs in the extremities pointing to lesions of the spinal cord.

We have obviously to deal with multiple lesions, involving a number of sites in the gray matter between the globus pallidus and the substantia nigra above and the lower end of the medulla oblongata below; the diencephalon, the mesencephalon, and the rhombencephalon are all involved. Moreover, this is almost entirely a motor syndrome; we have to deal, here, with a polio-encephalopathy, for the cells of the motor nuclei in the medulla, pons, and midbrain are involved, along with slight disturbances higher up (in the inter-brain).

Having reached the third stage of our diagnostic study, we next ask, What is the nature of this malady?

Are we dealing with a brain tumor? A cerebellar tumor might, by pressing from above, cause some such signs, but it would also give rise to increased intracranial pressure and to choked discs. So we can rule that out. A gliosis of the brain-stem could scarcely make such rapid progress in the two years, so it may be ruled out. Syringomyelia is ruled out by the mode of onset, as well as by the absence of sensory involvement.

Could the lesions be of vascular origin? A thrombosis of the basilar artery could conceivably give rise to this picture. But the syndrome is predominantly motor and it has progressed slowly over two years; if it were due to thrombosis it would have appeared more

suddenly, after an infectious process or an embolic process, and there have been no signs pointing to either.

Could the lesions be inflammatory in nature? Multiple (or disseminated) sclerosis is an inflammation that might be thought of. But the abdominal reflexes are present and, moreover, it would be extraordinary to find such extensive involvement of the brain-stem from multiple sclerosis without pyramidal-tract lesions and without symptoms in the trunk and in the extremities. We must not forget that we deal with a polio-encephalopathy. Could we be dealing with a rare form of the Heine-Medin disease (acute poliomyelitis of the bulbar type)? There was an outbreak of infantile paralysis in this city four years ago. But our patient's illness dates back only two years. Moreover, the paralysis in the Heine-Medin disease comes on all at once, and then there is gradual, partial recovery. Here the paralysis has progressed over a period of many months; it has been a chronic rather than an acute process. This finally brings us to a consideration of other forms of encephalitis involving the brain stem, of which there are many. In my opinion, we are dealing with an encephalitis that is subchronic, and probably with *epidemic encephalitis* (the lethargic encephalitis of von Economo).

There were ten cells in the spinal-fluid count and there has been a slight leukocytosis—signs that are suggestive of continuance of the inflammation. Moreover, the sugar content of the cerebrospinal fluid is high and this hyperglycorrachia is strongly suggestive of epidemic encephalitis.

This is about as far as we can go in the differential diagnosis at present, though the further course may give other clues that corroborate or refute our present conclusions.

The fact that the motility of the left face shows signs of improvement is encouraging. Not infrequently we see a great deal of lost function return after a time; unfortunately, all too often there are distressing sequels, especially parkinsonian signs.

As to treatment, we might find a case of lethargic encephalitis that has recovered and transfer some of the convalescent serum. Otherwise, we shall have to be content with general measures to improve the health and to increase the resistance to infection. Perhaps, in time, Doctor Ayer or Doctor Cobb will discover a more satisfactory therapy; let us hope so.

PULMONARY TUBERCULOSIS AND PROFOUND UNDER-NUTRITION, WITH COMMENTS UPON THE INSULIN-FATTENING CURE

DOCTOR BARKER.—Now that the first three patients have gone back to the wards, I must confess to you how relatively little can be expected from any form of therapy that may be applied to them. Far less discouraging from the therapeutic standpoint is the case of the patient about to be brought in. By modern methods of therapy and especially with the aid of the relatively new insulin-fattening cure, we are very hopeful that this next patient may be greatly helped. Before discussing the case you must hear Doctor Diack's summary of the clinical study that has been made.

DOCTOR DIACK.—This patient, a twenty-year-old billing clerk, entered the hospital complaining of cough, chills, and fever for the preceding nine days.

Past History.—He has been subject to colds all his life, and his tonsils and adenoids were removed in 1924. He says that, otherwise, he was well until three years ago, when he began to cough and "to go down hill."

Present Illness.—This began March 19th (about five weeks ago) with weakness, chills, and a severe pain in the back—symptoms that put him to bed. At that time his temperature was 102°. Two days later the fever and cough became much worse and a physician was called, who made the diagnosis of bronchopneumonia with pleuritic pain. When he entered the hospital here, this pain was still present.

Physical Examination.—The head, eyes, ears, nose, mouth and throat were negative. Over the left chest there was dulness downward from the level of the fourth thoracic spine and forward to the axilla and to the nipple line. Voice sounds and breath sounds were greatly diminished; tactile fremitus was absent. Temperature, 104.5°. Heart, rapid rate but otherwise normal. Abdomen, extremities and reflexes normal.

The left pleural cavity was tapped and 900 cubic centimeters of fluid removed. This fluid had a specific gravity of 1.020, and contained a large number of cells—all lymphocytes. No micro-organisms were seen. Since the tapping, his temperature has gradually declined until now it is normal. He has been on a diet of 3,000 calories. His pulse rate has remained accelerated, up to 120.

DOCTOR BARKER.—I had the opportunity of examining this patient this forenoon and I can corroborate the findings just reported. It is remarkable how the signs in the left chest have cleared up. The left thorax is expanding much better. You will notice, however, that the chest is funnel-shaped and that the man is characteristically of asthenic habitus, for in addition to the long flat chest he has a long neck and long gracile extremities and is markedly undernourished. Most persons of this asthenic habitus are also of schizoid temperament and persons of this habitus and of this temperament are particularly prone to be emaciated, to show low blood-pressure, and to be especially susceptible to tuberculosis. When tuberculosis develops in a schizoid asthenic, something (perhaps a diffuse intoxication) gives rise to a euphoria so that the mood becomes more like that of a syntonioic individual. It is very interesting to observe how a toxemia can temporarily change the disposition of a patient. The relative euphoria of many tuberculous patients has long been well known, despite the fact that many of them are of schizoid temperament. Still, Dr. Anita M. Mühl, a psychoanalyst, is of the opinion that the so-called "optimism of the tuberculous patient" is chiefly a myth or, at least, only a compensatory feature, for she found "depressions and suicidal trends in the unconscious" in the tuberculous women she studied.

The roentgenograms of this patient's chest are instructive. The left lung is involved extensively, and there is some involvement of the right. The fluid at the left base has not re-accumulated. The left apex, as you see, is extensively involved, much more so than the right.

This young man is sixty pounds under his calculated ideal weight. He has not been gaining in weight, despite the fact that he is eating liberally and now has no fever. The existence of this profound undernutrition is the reason why I have brought him before you, for I wish to discuss a new method of treatment for compelling a rapid gain in weight in such a case.

It goes without saying that he should be kept completely at rest and that he should be in the open air and exposed to sunlight—indeed, everything that the tuberculosis experts have taught us should be applied in order to increase his resistance to the tuberculous infection. If we can increase the weight of this man quickly to

normal it will be one of the greatest things we can do for him. He needs not only much vitamin A but also plenty of vitamin D, which we can supply in abundance through the administration of viosterol and by sunshine. He has not yet begun to gain weight, though he has no fever, is being kept completely at rest in bed and has received a diet containing from 2,500 to 3,000 calories. Why does he not gain?

During the past few years, a new method of increasing appetite and of improving the assimilative powers has been devised. In 1913, Falta suggested that some forms of obesity must be due to overactivity of the islands of Langerhans in the pancreas (hyperinsulinism). On the other hand, when the islands of the pancreas are diseased, as in diabetes mellitus, we see emaciation due to the using up of the carbohydrate reserves, and to loss of fat; the protein stores then begin also to melt away; this clinical picture is due to insulin insufficiency. As Falta has emphasized, "a functionally competent insulin-organ is necessary for a good nutritional state." It has long been known that it is difficult to fatten emaciated persons on a diet of protein and fat alone; carbohydrate must also be assimilated in order that the protein and fats of the diet may be adequately utilized. When insulin was finally discovered, it was all needed at first for the treatment of diabetics. But about six years ago, Faltá (in the *Wiener klinische Wochenschrift*, vol. 38, pp. 757-758) published the results of insulin treatment of three young women (ages twenty-one, twenty-five and thirty), who were very emaciated, complained of poor appetite and failed to gain weight, despite rest in bed and an abundance of easily digestible food. In addition to rest in bed and a liberal diet, they were given from three to five doses of insulin each day, ten units at each dose, one-half hour before the meal. This dosage was cautiously increased in one case to as much as 150 units of insulin each day and this to a person without diabetes! No change was made in the diet, except that it was abundant and that he insisted that at least a minimum of 30 gms. of carbohydrate should be taken at each of the five meals. Written instructions were given to each patient to take a lump of sugar or to eat some white bread in case symptoms of hypoglycemia appeared, though these almost never developed. The change that took place in these three young women was astonishing. From the first day,

all three patients developed a ravenous appetite, which was hard to satisfy. They ate from morning until night; an experimental bulimia was thus induced. Then he found that these patients gained from three to five pounds a week, whereas their weight charts had remained before on a horizontal level! The sharp upward rise of the weight record was almost startling. The enormous increase in the food intake caused no discomfort and all three patients rejoiced because of their great appetites. The only trouble he had was that the patients said it annoyed them that they could not swallow the food fast enough, even when it was in abundance before them. After three or four weeks he had to stop the insulin treatment in his second patient because she became obese. One patient gained 9 kilograms (20 pounds), a weight increase of almost 25 per cent. weight in thirty-nine days; another one gained 6.5 kilograms (14 1/3 pounds) in twenty-three days. In one day, one patient consumed three portions of tea (with three lumps of sugar to each cup), six rolls (a tablespoonful of honey with each roll), one-half bowl of potato salad, one portion of mashed potatoes, one large portion of cooked cereal, some sweet cakes, three large portions of meat, three bowls of soup containing vegetables and carbohydrates, 100 gms. of sausage, 100 gms. of bacon and one-quarter of a kilogram (half a pound) of butter! Before she began to take insulin it was with difficulty that she could be induced to eat anything at all!

On looking over the bibliography of the subject, I find reports of the beneficial effects of insulin in exophthalmic goiter with emaciation (J. Goffin, 1924; R. D. Lawrence, 1924) and in the undernutrition of certain infantile dystrophies (Pitfield and Marriott, 1923).

For the past three or four years I have been using insulin to compel a gain in weight in rundown, emaciated nervous patients. Others have found the method useful for the same purpose (*cf.* Appel, Farr, and Marshall, 1929). I have used only 8 or 10 units once or twice a day (given thirty minutes before the two principal meals) and apparently with as good results as when a larger dosage is employed. Some patients need 30 units or more each day, though most will gain well on from 16 to 30 units per day.

During this past winter, I have had to treat a young man who was sixty-five pounds under his ideal weight. He was given two

doses of 8 units each per day and in a few weeks he had gained forty-five pounds. Before taking insulin, he complained that he had no appetite but, afterwards, he admitted that he had a "splendid appetite." During the treatment he was kept in isolation from his family and, when he went home, his people scarcely recognized him. Another patient, under my care at present, gained seven and one-half pounds the first week and nine pounds the second week. But such rapid gain is exceptional; I am satisfied usually with a gain of from three to five pounds per week.

Is this gain in weight due merely to retention of water? No. The cells have increased water content undoubtedly, but, in addition, fat, carbohydrate, and protein are stored.

This application of insulin is one of the best ways we have of fattening emaciated people. It is being used both in this country and abroad in psychiatric hospitals, for it has been found most helpful in the treatment of patients suffering from mental depressions and inability adequately to eat. If you have not made a trial of this method, I advise you strongly to do so.

Let us now return to the patient before us. Should this insulin method be used in the treatment of tuberculosis even when, as in this man, emaciation is extreme? There has been great divergence of opinion. In tuberculosis in diabetics, some patients that received insulin had a flareup of the tuberculous process, supposedly due to hypoglycemic reactions. So some have thought that the existence of fever and of active tuberculosis were contra-indications to the use of insulin, even in diabetes. But more recent studies have shown that tuberculous diabetics can be safely treated with insulin, if reasonable precautions be observed. Some have feared the excitation of dangerous local exacerbations of the tuberculous process, but if pure insulin be used, there is probably but little danger. When there is no diabetes, the treatment of the emaciated tuberculous patient with insulin may be undertaken with confidence (*cf.* Combe-male, Gmez, and Breton, *Ann. de Med.*, vol. 26, pp. 480-500, Paris, 1929). But the dose of insulin should be small, 10 units once a day at the start. If this single dose be well borne, the dosage may be increased to 30 units a day divided into two doses, one dose thirty minutes before each of the two main meals. Every precaution must be taken against the occurrence of hypoglycemia. Let the patient

have a chocolate bar, lumps of sugar, and orange juice at his bedside. Do not give more than 30 units per day to a tuberculous patient. In some of these patients, it is best to give insulin for two weeks and then stop it for two weeks. Three such courses are often sufficient. I should like to see the treatment tried in this boy, and I hope that his tuberculosis will be arrested, and that before long he may be fifty or sixty pounds heavier than he is tonight.

QUESTION.—Do they retain this weight?

DOCTOR BARKER.—Yes. Most of them, in my experience, have retained it. It is also interesting that the appetite usually remains good after the insulin is stopped. In one of my cases, after a series of attacks of bronchial asthma, some fifteen pounds of the weight that had been gained was lost, but, after the asthma ceased, he quickly regained them. Of course, when the weight is approximately normal, we do not desire bulimia; we need then only enough appetite and food-intake to maintain normal weight.

QUESTION.—Does bodily strength increase?

DOCTOR BARKER.—Yes. Not only does bodily strength increase, but in many psychoneurotic patients, the nervous and mental state improves also. It is very interesting to watch an anorexic patient change to a bulimic patient; the change may occur within twenty-four hours!

DOCTOR CHRISTIAN.—Doctor Barker, as I sat among the audience, I was aware of several misconceptions. One of these is largely among the members of the students and internes, who do not know you as well as the older of us do. I want to assure them that you are not primarily a neurologist but a physician and internist who knows neurology.

I wish also to explain why Doctor Diack represented the house officers in giving the summaries of the clinical histories. This was a matter of chance. All of the patients shown were on Doctor Diack's ward. This was Doctor Barker's first day in the hospital, so he had seen only patients who were Doctor Diack's patients. I realize the splendid presentation of these patients by Doctor Diack, but I am sure the other two senior house officers would have done equally well in presentation.

Then I know that a large number in the audience have wondered

whether many of these delightful terms used by Doctor Barker are in the dictionary or not. I assure you if you have a recent and a large dictionary, you will find them all, and with them their definitions. From my own experience, I feel sure that you do not know the meaning of some of these words. So I advise you to go and look them up in the dictionary. If you do not find them, it will be because you have not got a recent enough edition.

It must now be clear to you why we invited Doctor Barker to come here this year. He is obviously what we might call a charmingly finished clinician. As such we have welcomed him, and I know that you, with me, have enjoyed his presentation of cases this evening.

Ward Rounds in the Peter Bent Brigham Hospital (Medical Service of Professor Henry A. Christian)*

A FEW OF THE CASES SELECTED FOR STUDY ON WARD ROUNDS, ILLUSTRATING THE METHOD OF PROCEDURE

By LEWELLYS F. BARKER, M.D., LL.D.

Physician-in-Chief *pro tempore* (April 21-28, 1931),
Peter Bent Brigham Hospital, Baltimore

DIABETES MELLITUS AND OBESITY WITH COMPLICATIONS

THIS patient presents multiple problems in diagnosis. The case is one that requires a comprehensive general diagnostic survey, in order that none of the details of the clinical picture may be overlooked, that the relative importance of the maladies existent may be determined, and that suitable therapy may be instituted and maintained. To be satisfied with a "snapshot" diagnosis in this case might be very detrimental to the patient.

CASE HISTORY (AS SUMMARIZED BY THE SENIOR HOUSE OFFICER,
DR. RICHARD H. YOUNG)

This patient, Lucy S., aged fifty, housewife, entered the hospital (service of Dr. Reginald H. Fitz) with the following *complaints*: headache; pain along the posterior aspect of the right leg; weakness; and weight loss of twenty pounds in the past three and one-half months.

Family History.—Not of significance.

Past History.—Usual childhood diseases without complications. In adult life, usually well except for (1) frequent attacks of tonsillitis, (2) influenza in 1918, (3) cholecystectomy in 1923 with pleurisy and pneumonia during

* Thanks are due to the Resident Physician, Dr. Marshall N. Fulton, and to his associates on the Resident Staff of the Hospital for help in the compilation of these notes, which have been subsequently revised by the writer.

convalescence, and (4) asthmatic seizures and severe hay fever during the past five years.

Present Illness.—This is said to have begun three and one-half months ago with a severe attack of influenza, fever of 104°, cough, sore throat and diarrhea. The patient was sent to the Boston City Hospital where she was told that she had diabetes mellitus. On inquiry, it was learned that frequent urination and nocturia had begun eight years earlier. She remained only one day in the hospital, convalescing from her influenza at home.

Since then she has suffered from pruritus, headache, paresthesias of the tips of the fingers of the right hand, progressive weakness, and loss of weight. In addition to these complaints, she states that, five months ago, she fell, and, afterwards, had a painful right knee. Besides this pain in the knee, there has been severe pain, at times lightning-like, beginning over the right sacroiliac region and extending down the posterior aspect of the right leg. For the past two or three weeks she has felt very weak, has had drenching night sweats, palpitation, and some five "fainting spells." The loss of weight during the present illness has amounted to about twenty pounds. Seen first in the Out-Door Department, she was sent into the hospital for study and treatment.

Physical Examination.—A well-developed, obese female, restless, reclining in bed. Skin, warm and moist, with a telangiectatic area over the upper front chest.

Pupils react to light and on accommodation. Ophthalmoscopic examination negative, except that the retinal arterioles are somewhat small in caliber and tortuous; there is definite nicking of veins where crossed by arterioles. Slight nasal obstruction. Tonsils markedly enlarged, boggy, but without signs of acute inflammation, though plugs could be expressed from the crypts.

Anterior-posterior diameter of chest increased; respirations labored; hyperresonance on percussion; on auscultation, sibilant and sonorous rhonchi over both lungs and coarse moist râles audible at the right base, posteriorly.

Heart not enlarged; soft systolic murmur audible at the base; A, slightly accentuated. Blood-pressure 155/95.

Abdomen very obese; wall weakened to the right of the cholecystectomy scar, with definite ventral hernia. Extremities negative, except for hypalgesia and hypesthesia of the distal portions of the fingers of the right hand; over the index finger of the right hand there is almost complete analgesia and tactile anesthesia.

Laboratory Reports.—*Blood.*—Red blood-cells, 5,170,000; Hb., 70 per cent.; white blood-cells, 1,950.

Urine.—Specific gravity normal; slight albuminuria and glycosuria; no diacetic acid; no casts. On admission, phthalein output 65 per cent.; blood sugar 226 milligrams per cent.

Course in the Hospital.—The diabetes has thus far been fairly well controlled; the blood-sugar content has fallen to 144 milligrams per cent. With rest in bed and digitalis, the albumin disappeared from the urine. Routine allergic skin tests showed the patient to be sensitive to wheat globulin, chicken feathers and goose feathers.

X-rays of the sinuses showed slight clouding of the right ethmoid cells and of the right antrum; X-ray of the right knee shows a lipping of the joint margins (hypertrophic arthritis).

DISCUSSION OF THE CLINICAL FINDINGS

After hearing the history and making a physical examination myself, I would summarize the diagnosis as follows:

- (1) Diabetes mellitus (with glycosuria and hyperglycemia).
- (2) Mild diabetic neuritis (with hypesthesia of the distal portion of the right hand and in the course of the right sciatic nerve).
- (3) Focal infections:
 - (a) Chronic tonsillitis;
 - (b) Chronic sinusitis (right ethmoid cells and right antrum).
- (4) Obesity (forty pounds overweight) with obesity-cardiopathy and systolic murmur at the apex.
- (5) Allergic state (with history of hay fever and bronchial asthma); the allergens are now under study.
- (6) Chronic hypertrophic arthritis (both hips and right knee).
- (7) Postoperative ventral abdominal hernia.

This patient needs a period of hospitalization with thorough education as to dietetic measures to be observed to keep the diabetes under control and to reduce the weight. For a time, the strict Evans anti-obesity diet might well be followed; later, after the weight has become normal, the diet should consist largely of protein, fat, and 5 per cent. vegetables, with enough calories to maintain normal weight. This dietetic regimen may prove to be very helpful in overcoming also the diabetic neuritis and the obesity-cardiopathy; it may prove to be ameliorative for the hypertrophic osteo-arthritis. The foci of infection should be watched and, if necessary, removed later on. The asthma and hay fever might be prevented by suitable desensitization.

**ACUTE RHEUMATIC FEVER IN A SCHOOL GIRL, WITH
THROMBO-ENDOCARDITIS, PURPURA HEMOR-
RHAGICA, SPLENOMEGALY, AND
SECONDARY ANEMIA**

The next patient has had fever, fleeting joint swellings and pains, enlargement of the spleen, anemia, and purpura. After the Senior House Officer has told you of the development of the symptoms and signs and of the clinical abnormalities still existent, we

shall try to arrive at a decision regarding the nature of the process with which we have to deal.

CLINICAL HISTORY (SUMMARIZED BY DR. RICHARD H. YOUNG)

This patient, Beatrice S., a sixteen-year-old high-school graduate, entered the hospital (service of Dr. Reginald H. Fitz) complaining of pain and swelling of the joints.

Family History.—Irrelevant, except that her mother died of heart disease at the age of thirty-four.

Past History.—She remembers no childhood diseases and, until her present illness, has been a strong and active child, except for frequent head colds, one attack of otitis media, and two operations (tonsillectomy and adenoidectomy in infancy; appendectomy in 1920). She gives no earlier history of rheumatic fever, growing pains, chorea, nose-bleeds or vomiting.

Present Illness.—About four months ago the patient felt somewhat run down. Three months ago she was put to bed because of fever, malaise and a reddened, swollen, and painful left lower leg and ankle. This inflammation soon died down but her right wrist suddenly became very painful and remained so for a period of one and one-half weeks, when the pain there grew less, only to be followed by recurrence of the pain in the left ankle. Concomitantly, she had fever and was confined to bed for another two weeks, after which she felt well enough to be up and about. For the next three weeks she felt well, except for fleeting joint pains.

Two weeks before admission, she had a gastro-intestinal upset, with malaise, nausea and constipation; this was followed by pain, redness, and swelling of the left knee, necessitating bed rest; these symptoms persisted until entrance to the hospital. Except for occasional palpitation, there have been no cardio-respiratory symptoms.

Physical Examination.—On admission, fairly well developed and well nourished. Face and mucous membranes pale. No apparent pain or distress. Pupils, conjunctivae, and eyegrounds normal. Tonsils have been cleanly removed. Pharynx, moderately inflamed and reddened.

Heart's apex impulse forceful. On palpation, a coarse, presystolic thrill over the apical region. Heart rate accelerated, with regular rhythm; presystolic rumble ending in an accentuated first sound and a loud systolic murmur heard best at the apex; P₂ markedly accentuated; no aortic diastolic murmur. Both the systolic and diastolic readings are lower than normal.

Abdomen, well developed and symmetrical. Tenderness and voluntary spasm on fairly deep palpation in the left upper quadrant. Though no mass could be felt, there was definite increase in the area of splenic dullness.

Extremities show equal and active reflexes; no evidence of peripheral edema.

Laboratory Findings.—*Blood.*—Red-cell count, on admission, 3,750,000; hemoglobin, 70 per cent.; white-cell count, 7,200, with 78 per cent. polymorphonuclears.

Urine.—Normal; phthalein output, 78 per cent.

Blood Cultures.—Two have been made, both of which were negative after twenty-one days.

Course in the Hospital.—At the end of the first week of her hospital stay, the pain in the left upper quadrant suddenly became very severe. There was a concomitant increase in her temperature, which rose from 99° to 102°. During the next ten days, she was very uncomfortable, showing a diurnal variation in her temperature, the fever in the afternoon occasionally rising to 104°. During this period, a fairly large mass could be felt in the left upper quadrant; it was believed to be spleen.

Two weeks after admission, the tip of the index finger of the left hand suddenly became reddened, tender, and slightly swollen. On the following day, the fifth finger of the right hand became similarly affected and, later, the first finger of the right hand. These signs soon disappeared, but they were followed by arthralgias of the hip, knee and wrist on the left side.

Ten days ago, the patient developed slight swelling of the right parotid gland, but the temperature fell to normal and remained normal for four days.

The latest development has been the appearance of a dollar-sized, reddened, tender area over the dorsum of the left foot, and this has been accompanied by an increase in temperature. Yesterday, a few reddish areas in the right conjunctival sac, suggestive of petechiae, appeared.

During her hospital stay, the systolic murmur has changed somewhat in intensity, and has become more musical.

DISCUSSION OF THE DIAGNOSIS AND THERAPY

Her hands are cold, clammy, and slightly cyanotic. Facies, sallow and pale. I can find no petechiae, today, in the conjunctivae. One tooth, the left upper molar, looks suspicious; it should be X-rayed. The lymph-glands in the neck are not enlarged and there is no struma. The glands in the left axilla are palpable; one of them, indeed, is quite large; the inguinal glands are not enlarged. On listening to her heart, today, I find the signs of outspoken mitral insufficiency (loud blowing systolic murmur, transmitted to the axilla; P₂ markedly accentuated). It is interesting that the signs of mitral stenosis, described as present before, are not in evidence today.

The area of splenic dulness is still definitely increased; she holds herself so tense on palpation that I cannot feel the notch. There is a marked purpuric discoloration of the dorsum of the left foot. I can feel no subcutaneous fibroid nodules anywhere.

The polyarthritides (flying from joint to joint), the remittent fever, the development of a lesion of the mitral valve, and the purpura make the diagnosis of acute rheumatic fever with purpuric manifestations certain.

Enlargement of the spleen is sometimes met with as one of the visceral lesions in purpura, but, because of the thrombo-endocarditis of the mitral valve and of the sudden severe pain that she felt in the left upper quadrant, we must keep in mind the possibility of splenic infarction due to embolism.

I have leaned to the idea that rheumatic fever is due to some unknown virus, about the nature of which we know, as yet, almost nothing. In connection with this case, you should review the excellent research work upon acute rheumatic fever that has been carried on at the Hospital of the Rockefeller Institute in New York by Dr. H. F. Swift and his associates. I would also call your attention to the interesting article by my colleague in Baltimore, Dr. W. S. Thayer, on acute rheumatic diseases of the heart; it appeared in the *Bulletin of the Johns Hopkins Hospital* in 1925. Your own Dr. Paul D. White has reported a case in which heart block was the first sign of rheumatic fever.

When considering the treatment of this patient, we must plan to relieve the pain, to care for the strength of the heart muscle, and to get rid of the infection.

Salicylates will ease the pains promptly as they recur, but will probably not shorten the duration of the illness.

To increase her resistance to infection, one might give her lots of vitamins A and B in her diet.

One might also investigate the calcium content and the clotting time of the blood, because of the purpura.

For overcoming the secondary anemia, the use of iron and ammonium citrate should be helpful. She will doubtless recover from her acute infection but there will be a residual and permanent lesion of the mitral valve.

**ACHYLIA GASTRICA, CHRONIC DIARRHEA, ANEMIA
WITH HIGH COLOR INDEX, AND STOMATITIS,
OCCURRING IN A PATIENT WITH CON-
GENITAL HYPOTHYROIDISM**

As we gather around the bed of this patient, we see in her facies, immediately, certain striking peculiarities that direct our attention to the endocrine system. A glance at the hands of the patient is corroborative of the impression we form from the facial character-

istics. Let us listen to the clinical history, after which we may discuss the endocrinopathy that is manifest, along with the other findings.

CLINICAL HISTORY (SUMMARIZED BY DR. RICHARD H. YOUNG)

This patient, Florence R., a forty-four-year-old housewife, entered the hospital (service of Dr. Reginald H. Fitz) recently, complaining of "troublesome diarrhea."

Family History.—Her father died of cerebral hemorrhage at sixty. Her mother died suddenly of heart disease at thirty-eight. One aunt has diabetes.

Past History.—The patient had the commoner childhood diseases, which ran a normal course without complications. During adult life she has been well and active, until three years ago, when she was bothered by constipation, and this gradually became ever more obstinate. During the past year, she has had dyspnea on exertion and has noticed, occasionally, swelling of the ankles. She states that she has less thirst and appetite than formerly, and that her skin has become increasingly rough; the latter symptom she attributes to the use of a poor grade of soap. During the past summer, the constipation became extreme. In September, she first noticed paresthesias—numbness and tingling in both hands. Two weeks before her first admission to the hospital in November, 1930, her local doctor had given her a cathartic (supposedly cascara), which was followed by diarrhea that persisted, and also by a distressing stomatitis and gingivitis.

On physical examination, at that time, the positive findings included dwarfism, obesity, dry thick skin, narrow lid slits, scanty eyebrows, thick lips, stomatitis, pads of fat above the clavicles, enlargement of the heart, low blood-pressure, umbilical hernia, and hyporeflexia of the extremities.

Laboratory studies revealed a moderately severe anemia with high-color index, an achylia gastrica, occult blood in the stools, and a slightly retarded basal metabolic rate (minus 15).

In a teleroentgenogram, the heart shadow was enlarged to both sides. After a barium enema, a smooth colon with certain constrictions was interpreted by the roentgenologist as typical of colitis. (Fig. 1.) The proctoscope, introduced for a distance of eighteen centimeters, revealed a reddened mucous membrane with small bleeding points and with occasional small areas of grayish exudate.

During her two months' stay in the hospital last winter, she had a continuous slight fever, tachycardia, and diarrhea; the latter symptom did not respond to any of the forms of medication tried. Because of her hypothyroidism, she was given small doses (0.030 Gm. b.d.) of thyroid extract, and this was followed by an increase in the pulse rate. Repeated X-rays of the heart showed some decrease in its size. When she was discharged on January 16, 1931, her condition had improved very much; the skin was softer and less scaly, her speech had quickened and was less scanning in type, and the diarrhea had improved somewhat, in that the number of stools had been reduced to two or three per day and they were better formed.

FIG. 1



X-ray film of colon of the patient Florence R. Note the narrowing of caliber in various places, as well as the abolition of the haustra coli.

On return to her home, she remained very well until March 1, 1931, when, on attempting to go down stairs alone in order to surprise her family, she accidentally tripped and fell to the bottom, landing on her buttocks. This apparently precipitated an attack of diarrhea and, afterward, she had from ten to twenty watery bowel movements daily until she re-entered the hospital. She stopped taking thyroid extract and tried bismuth powders to combat the diarrhea, but without effect.

Present Condition.—Physical examination now yields practically the same findings as noted before, except that the obesity is less marked, the skin is softer, smoother and less scaly, and the heart is of approximately normal size. The blood-pressure is 102 millimeters systolic, 74 millimeters diastolic. Basal metabolic rate is now minus 20.

Since admission, the diarrhea persisted for some four weeks, when she was given dilute hydrochloric acid; except for two days when she received 6 milligrams of thyroid extract thrice daily, the diarrhea was thus fairly well controlled.

The stomatitis and the gingivitis, which have also been very persistent, are now yielding to the local treatment instituted by the dental house officer. He has made three applications of 10 per cent. chromic-acid solution and has encouraged the frequent use of a mouth-wash containing sodium perborate.

DISCUSSION OF THE DIAGNOSIS AND FURTHER TREATMENT

This patient presents a text-book picture of mild congenital hypothyroidism, even to the umbilical hernia, though there appears to be no marked obtunding of the mental state. The sparseness of the supercilia lateralward, which we see here, and the enophthalmos with narrow lid slits, are common findings in long-continued hypothyroidism. The tongue, too, is rather large and is pale. I cannot definitely feel the thyroid gland. The skin is dry and coarse and the rugae are increased. The hands are short, and the lunulae (or white crescents at the bases of the finger-nails) do not show. There are spots of brownish pigmentation over the body. The heart may not be enlarged but merely appear to be because of its transverse position, due to elongation of the aorta. No masses can be felt in the abdomen. The spleen is not palpable, nor is there any increased splenic dulness. The liver edge is not palpable. The toe-nails are markedly elongated and atrophic. The knee-jerks are active.

The patient formerly had an anemia with high-color index; there is an achylia gastrica, and she has chronic diarrhea.

One ought to keep in mind the possibility of an earlier mercurial intoxication, in view of the fact that the stomatitis and

gingivitis appeared soon after an unknown purgative was administered. It is interesting that the diarrhea became much less marked after the administration of dilute hydrochloric acid; you will recall the frequency of so-called "gastrogenous diarrhea" in association with achylia gastrica.

Her endocrinopathy is probably a congenital affair, and consists mainly of hypothyroidism.

The Resident Staff of this hospital must be very familiar with "the family tree of achylia gastrica" described by Doctor Christian; and this patient has achylia gastrica, stomatitis, anemia with high-color index, and paresthesias of the extremities!

In the *treatment* of this case, hydrochloric acid with the meals, a bland diet with caloric value corresponding to what is needed to secure ideal weight, the use of liver, liver extract and ventriculin, and of iron and ammonium citrate, would seem to be indicated. In addition to the liver and liver extract to be given by mouth, one dose per week might be given intravenously, since Doctor Castle has recently shown us how to do this safely. The dentist should continue the treatment of the gums. Each night, a little olive oil or some other bland emollient might be applied to the harsh, dry skin. A course of anusol suppositories—one every night for a week—would help to diminish the hemorrhoids.

If there should be a return of the rectal catarrh, I would recommend the use of suppositories of the following formula that I learned from O. Schirmer:

R

Atrop sulph.....0.0005 Gm.

Menthol.

Tumenol.....āā 0.1 Gm.

Bism. subgal.....0.2 Gm.

Ol. theobrom. q.s.

Ft. Suppos. No. 1. Mitte talis No. xii.

One of these suppositories introduced into the rectum morning and evening for a few days will often give marked relief in catarrhal proctitis.

The patient should receive a little thyroid extract (to be given cautiously), beginning with one-half grain once a day, and increasing to the limits of tolerance, after which a smaller dose could be administered for two or three weeks of each month.

SEVERE SECONDARY ANEMIA OF POSTHEMORRHAGIC ORIGIN IN A PATIENT WITH MITRAL STENOSIS WHO HAS EXHIBITED EVIDENCES OF CHARACTER DEFECTS

I am told that the next patient suffers from an interesting form of anemia, that she has a valvular disease of the heart, and that she has lived in a manner that betokens some abnormality of the affective-conative side of her nature. After we have heard her history and the findings since entrance, I shall discuss the diagnosis and the treatment.

SUMMARY OF CLINICAL HISTORY (DR. RICHARD H. YOUNG)

This patient, K—— G., a thirty-one-year-old, American-born housewife, entered the hospital (service of Dr. Reginald H. Fitz) three days ago, complaining of shortness of breath on exertion, and of numbness and tingling of the hands and feet.

Family History.—One grandmother died of cancer, and an aunt of pulmonary tuberculosis. Her mother has always been rather pale, and of a yellow tinge.

Past History.—Measles and whooping cough as a child; chorea at the age of twelve, for one and one-half years; scarlet fever ten years ago; and recurrent attacks of tonsillitis up to three years ago. She is married, and, at the age of twenty-one, had had three pregnancies within twenty-seven months. After the birth of the third child, she suffered a profuse uterine hemorrhage, which required a transfusion of 1,750 cubic centimeters of blood from her father. Following this pregnancy, she became subject to colds, felt run down, was pale, and had periods of malaise and lassitude.

During the third or fourth month of the subsequent pregnancies, she would become pale and weak, would feel numbness and tingling of her hands and feet and would complain of palpitation. She would go to bed and remain there until after delivery, but her numbness and tingling would not disappear until three or four months post-partum.

Her marital career has been stormy. Her family and husband state that she has been sexually promiscuous; only last Fall she was charged with adultery. She has been separated from her husband for six months and has, presumably, been living with another man.

Present Illness.—Three months ago she had an attack of "grippe," characterized by headache, fever, cough, pain in the chest, ringing in the ears and general malaise. This attack lasted for three weeks, during which time her menstrual flow continued, sometimes, she says, "pouring out as from a faucet," when she got out of bed. That was the first time that the menstrual flow had not been preceded by epistaxis. Following recovery from this illness, she

remained pale and dyspneic, her lips were blue, and she complained of palpitation of the heart and of numbness and tingling of her hands and feet.

During the past month, there has been an increase of pallor and of lassitude, and she has become very thirsty. Her ankles have begun to swell, at first only in the evening, but now after she has been standing for only an hour. Recently, she has noticed puffiness of her face. She has not complained of anorexia, nausea, vomiting, diarrhea, or sore tongue and there has been no evidence of ataxia or spasticity.

Physical Examination.—A well-developed and fairly well-nourished young woman, who lies listlessly in bed and looks tired. Skin pale, of a faint orange tint, smooth and dry; mucous membranes also very pale. Pupils equal, and regular in outline, reacting well to light and on accommodation. There is a perforation of the nasal septum. Patient is edentulous, with upper and lower dentures. Tongue pale, somewhat smooth, but not definitely atrophic. Heart moderately enlarged, with a loud, harsh, systolic murmur, best heard at the apex. Blood-pressure, 113/85. Abdomen well developed and symmetrical, without masses or spasm; no palpable enlargement of liver or spleen. In the extremities there is slight hyper-reflexia without clonus, but no Hoffman, Babinski, Oppenheim or Gordon signs can be elicited. There is no diminution of vibratory sense, and the sense of position is normal.

Laboratory Reports.—*Blood.*—Red blood-cells, 1,950,000; hemoglobin, 35 per cent.; white blood-cells, 6,700. Differential count: 67 per cent. polymorphonuclears; 24 per cent. lymphocytes; 9 per cent. monocytes; no eosinophiles or basophiles. Icteric index, 4. Blood iron, 13.3 milligrams per 100 cubic centimeters of whole blood; hemoglobin 4.42 gms. per 100 cubic centimeters. Blood group, IV. Bleeding time, by skin puncture and one-half-minute blots, was two and one-half minutes; clotting time, by skin puncture without squeezing, six minutes. Total protein of blood, 6.34 (albumen 4.7, globulin 1.34). A careful study of the fresh blood slide showed marked variation in the size and shape of the red cells, with a tendency to microcytosis, although there were a few macrocytes, some of which showed polychromatophilia. A moderate number of elongated oval forms and of fragmented cells were seen. The blood-platelets were normal or slightly increased in numbers and many of them appeared to be abnormally large. The white blood-cells did not appear to be abnormal.

Urine.—Negative.

Stool.—Contains occult blood (+++benzidine, +guaiac), but there are no free fat, starch, gross mucus, ova nor parasites.

Smear of exudate from cervix uteri showed abundant pus-cells, but no Gram-negative intracellular diplococci.

Stomach Contents.—After the usual Ewald test-meal and histamin, the free hydrochloric acid was as high as 37 acidity per cent., and combined hydrochloric acid as high as 52 acidity per cent.; rennin and pepsin present.

Course in Hospital.—Since admission, the patient has had slight fever (100° F.) and there has been a slight increase in the pulse rate. The anemia is being treated with a diet that includes 250 gms. of liver pulp daily and with Blaud's pills (0.6 gm.) thrice daily.

DISCUSSION OF THE HISTORY AND THE CLINICAL FINDINGS

This patient is obviously very anemic, and a low-grade fever is often associated with an anemia of this degree. The peculiar blueness of the thenar eminence may be due to localized venous dilatation. The anemia is of secondary type and is probably the result of recurring epistaxis and of the severe uterine bleedings. There is one particularly disturbing factor with regard to the anemia in this case, namely, the lack of blood-regenerating capacity. One would hope for an active bone-marrow in order that the blood may be restored. As a rule, in these cases, there is, during recovery, a leukopoietic response first, followed later by an erythropoietic response.

On examination of the heart, I hear a loud rumble during diastole at the apex followed by a snapping first sound. At the base, P₂ is louder than A₂. There is undoubtedly an organic valvular lesion (mitral stenosis). I can find no evidence of aortic disease. The veins of the legs are slightly dilated, but there is no edema now.

Though the spleen is not enlarged, I would suggest a blood culture (because of the fever) to rule out a *Streptococcus viridans* infection.

The reflexes are approximately normal; despite the paresthesias complained of, there can be no extensive funicular myelopathy.

There have been economic difficulties and serious social conflicts in the life of this patient. Doctor Young has referred to the evidences of character defects. In view of her high standing in school, she probably has had involvement of the affective-conative part of the psyche, without much involvement of the cognitive part.

For *therapy*, I strongly recommend transfusions of blood to be repeated weekly until the hemoglobin has reached 85 per cent. or more. The diet should include liver and she should receive iron, either in the form of Bland's pills or of iron and ammonium citrate; it might be well to give some arsenic also.

The source of the hemorrhages from the nose should be located and appropriate local treatment instituted. In addition, the abnormal gynecologic condition should be studied and treated. If the uterine hemorrhages cannot be stopped by curettement or other means, I would advise hysterectomy.

Finally, the industrial and social situation should be carefully

considered, since there would seem to be great need of improvement of the economic, the social, and the ethical status of this patient. Perhaps, during her convalescence, we can interest the Social Service Department and other welfare organizations in this case.

Subsequent Note.—The Resident Physician, Dr. Marshall N. Fulton, wrote me in June (two months after I saw the patient), that a blood transfusion was given and, on April 29, Doctor Homans excised the uterus. She was given a roborant diet and iron tonics and, two weeks later, her red-cell count had risen to 3,300,000 and her hemoglobin to 60 per cent. He adds: "I doubt if we improved her moral attitude perceptibly, but she will have no more children."

TERMINAL STAGE OF ADENOCARCINOMA OF THE JEJUNUM WITH RETROPERITONEAL AND CEREBRAL METASTASES; COMMENTS UPON A METHOD OF INSURING EUTHANASIA

The patient before us has been under observation at intervals during the past four years. She has undergone several surgical operations for neoplastic disease and she entered the hospital some twelve days ago with symptoms pointing to further metastatic involvement. The case will afford opportunity for discussion of a well-tested method of inducing euthanasia.

SUMMARY OF THE HISTORY (DR. RICHARD H. YOUNG)

This patient, Lillian C. R., is a forty-one-year-old housewife, who entered Ward E-Main of the hospital (service of Dr. Reginald H. Fitz) on April 10, for medical observation, as she complained of severe headache, dizziness, and stiffness and shaking of the right lower extremity." There is no family history of disease.

History of Previous Admissions.—This is the fifth admission of the patient to this hospital; she spent three periods on the Surgical Service, and one period on the Medical Service, earlier. To understand her present condition, it is necessary to review the findings on these several occasions.

The patient had been well and active until April, 1927, when she suddenly felt severe epigastric pain coming on half an hour after the evening meal. This pain lasted for half an hour and was followed by nausea and vomiting. There was no jaundice and no blood was noticed in the stools or in the vomitus. During the next four months (up to the time of her first surgical admission), she had noticed that, after eating solid foods, there were peristaltic waves across her abdomen, nausea and vomiting occurring shortly thereafter. Though she

limited her diet largely to fluids, the intermittent pain followed by nausea and vomiting continued and she lost twenty pounds in weight during the four months.

On her *first admission to the Surgical Service*, in June, 1927, her pulse, temperature and respirations were all normal. She was well developed and fairly well nourished, despite the history of weight loss. There was no abdominal distension and no masses were felt. The blood and the urine were normal. An X-ray series of the gastro-intestinal tract, however, established the diagnosis of upper jejunal obstruction. There was almost complete retention above the constriction in an examination made twenty-four hours later; in addition, reverse peristaltic waves had forced the barium back into the stomach.

At operation, the surgeon found thickening and dilation of the stomach and duodenum, and, about eighteen inches below the ligament of Treitz, an annular constriction of the jejunum could be felt. This growth (with the adjacent mesentery) was resected, and a side-to-side anastomosis was made. There was no evidence of involvement of the adjacent lymph-nodes.

The pathologic examination of the excised tumor showed a constricting annular mass, the lumen of which admitted a probe one millimeter in diameter. Microscopic sections showed adenocarcinoma with involvement of the muscular coat, the serosa and the adjacent mesentery.

The patient made an uneventful postoperative recovery, and remained symptom-free for four months, that is, until November, 1927, when a recurrence was suggested by persistent dull pain in the lower abdomen. During the next three weeks, the pain became very severe and the patient, herself, felt a hard mass in the lower abdomen. There was no constipation, the stools did not look abnormal, and there was no loss of weight.

On her *second admission to the Surgical Service*, in December, 1927, she had, in addition, begun to complain of frequency of urination and of slight bleeding from the womb. On physical examination, a fixed, tender, firm mass was palpable in the lower abdominal cavity; it lay apparently between the uterus and the bladder. Exploratory laparotomy revealed a large retroperitoneal mass, which displaced the adjacent viscera. This mass measured about twenty centimeters in all directions. Following the removal of the greater portion of the mass, there was considerable postoperative shock. She had to be transfused, but she responded well and was discharged, apparently in good condition.

Pathologic examination of the excised retroperitoneal mass showed a structure similar to that of the primary growth.

On completion of a course of deep X-ray therapy in February, 1928, the patient's condition seemed to be excellent. She then remained well for five months and gained weight.

In July, 1928, she suddenly felt a severe pain in the right lower quadrant. On a *third admission to the Surgical Service*, a large mass could be felt on bimanual examination and there was exquisite tenderness in the right lower abdominal quadrant. Exploratory laparotomy revealed a distended colon, with constriction of the lower part of the sigmoid. Accordingly, sigmoidostomy was performed, a metastatic retroperitoneal tumor that had pushed the pelvic viscera forward was removed; unexpectedly, the existence of an acute appendicitis was also demonstrated, and the appendix was excised. A later attempt

to close the colostomy opening proved to be unsuccessful. The patient was discharged in August, 1928, in fairly good general condition.

During the next six weeks, the patient developed a productive cough. On her *first admission to the Medical Service* (in September, 1928), physical signs, roentgenograms, and bronchoscopic examination indicated the existence of a lung abscess. She improved, however, while in the hospital and repeated X-ray plates made in the Out-Door Department showed a clearing up of the lung process.

The case up to this point has been reported by Dr. Francis Newton and Dr. Richard Buckley in the *New England Journal of Medicine* of February 6, 1930, as one of two cases of primary adenocarcinoma of the jejunum.

After December, 1928, when the patient felt quite well, and was up and around the house, she gained fifty-two pounds, and continued in good health until December, 1929, when for two weeks she had some pain in the lower abdomen, which subsequently disappeared. Otherwise, she remained symptom-free until one month ago, when she began to have moderately severe frontal and temporal headaches on the right side. These headaches became more frequent and eventually constant, so that she was unable to obtain relief by the use of ordinary analgesics, and only partial relief from morphine.

Two weeks before the *present admission to the Medical Service*, she had a dizzy spell. Two days before entry, she became incontinent of urine and remained in bed. On the day before admission, on attempting to walk, her husband noticed rigidity and shaking of her right leg. There have been no mental symptoms except depression and some impairment of the memory. For the past twelve months, the patient has consumed between a pint and a pint and a half of whiskey each day.

Physical Examination.—The patient shows no evidence of weight loss, but is stuporous and hypnoleptic. The pupils react to light and on accommodation. The optic discs are of normal color, size and shape, except for slight haziness of the temporal margins, and the retinal veins are slightly overfull. The abdomen is symmetrical and shows the scars of the previous operative procedures; the colostomy opening functions satisfactorily. On bi-manual examination, the pelvis is found to be filled with an irregular, non-tender, hard mass, with the cervix fixed anteriorly and to the left. Neurologic examination is negative except for bilateral hyper-reflexia and an equivocal Babinski on each side.

Laboratory Reports.—*Blood.*—Red blood-cells, 4,150,000; hemoglobin, 70 per cent.; white blood-cells, varied from 6,100 to 9,000, with from 70 to 74 per cent. polymorphonuclears. Wassermann reaction, negative.

Urine.—Specific gravity, 1012 to 1018; no albumin; no sugar; sediment contains many red and white blood-cells (in catheterized specimen).

Stool.—Negative.

Cerebrospinal Fluid.—Clear, colorless, under normal pressure; five lymphocytes; globulin+++; colloidal gold curve, 5555543100; total protein, 135 milligrams per cent.; Wassermann, negative.

Roentgenograms of the Skull.—No signs of increased intracranial pressure, but there is an indistinct mottling of the frontal bones, not definitely characteristic of metastases. The sella is somewhat atrophic. Otherwise, the findings are normal.

Course in the Hospital.—The stuporous condition has persisted and it has been very difficult to arouse the patient. There have been occasional epileptiform seizures, of short duration, which have involved the right half of the body.

DISCUSSION OF THE DIAGNOSIS AND TREATMENT

The existing symptoms—headache, stupor, epileptiform seizures, pallor of left optic disc, and altered cerebrospinal fluid—are highly suggestive of intracranial (and perhaps cranial) metastases. The metastatic mass in the retroperitoneal region, rather than the primary jejunal neoplasm, may have been directly responsible for the cerebral metastases. One must not lose sight of the possibility of infection with the virus of epidemic encephalitis, because of the drowsiness and other cerebral symptoms, but metastatic neoplasm seems more probable.

The *treatment* from now on will consist largely in ensuring quiet euthanasia. For this purpose, I have found the administration of Schlesinger's solution most helpful. The formula of the solution is as follows:

℞	
Scopolamin. hydrobrom.	0.0025 Gm.
Dionin.	0.4 Gm.
Morph. hydrochl.	0.2 Gm.
aq. dest.	10.0 Cc.

Of this solution, I give, at first, five minims in the morning, and seven minims at night (hypodermically). The dose may be gradually increased to ten minims, and in the later stages, as many as four doses in twenty-four hours may be administered. In my experience, the effects are far more satisfactory than with morphine alone.

Further surgical intervention in this case would not seem to be justifiable. The family should be informed as to the nature of the situation and the rationale of the therapy. The nursing staff can be most serviceable in the further care of this patient.

Subsequent Note.—A letter from the Resident Physician, Dr. M. N. Fulton, reports that the patient was kept entirely comfortable with injections of Schlesinger's solution until her death on May 8, 1931. Unfortunately, the family refused permission for autopsy, despite requests made by several members of the Visiting Staff.

gests bronchiectases; they might easily be present, as the patient has emphysema and chronic bronchitis. We should not forget the possibility of neoplasm.

- (2) *Valvular cardiopathy* (mitral stenosis, mitral insufficiency, and, possibly, aortic stenosis) with *cardiac hypertrophy* and with *mild circulatory insufficiency* (tachycardia; dyspnea; but no edema).
- (3) *Bamberger-Marie disease*, with lesions thus far limited to swellings (Figs. 3, 4, and 5) of the soft parts of the fingers and toes (*acropachia*); an ossifying periostitis may become demonstrable later, as it frequently develops in association with chronic intrathoracic infections.
- (4) *Secondary anemia* (red cells, 3,650,000; Hb., 70 per cent.) with leukocytosis (13,200).
- (5) *Slight nephropathy* (with casts in the urine).
- (6) *Undernutrition* (twenty-five pounds below calculated ideal weight for height).
- (7) *Kyphosis of thoracic spine*.
- (8) *Faulty hygiene* (caffeinism; alcoholism; venereal infections; dietetic errors).

It is interesting that, on admission, practically this whole multidimensional diagnosis was made by the Senior House Officer, Doctor Buhrmester.

The patient will, of course, be kept under close observation, and further studies may possibly reveal other diagnostic data that will be helpful.

The *therapy*, at present indicated, would seem to be as follows:

- (1) *For the circulatory system*: Rest in bed; Karrell diet for four days and afterwards five small meals daily with limitation of fluid intake to 1,200 or 1,500 cubic centimeters; magnesium sulphate each morning; provision for adequate sleep; digitalization.
- (2) *For the respiratory system*: Thoracentesis, as required; inhalations; potassium iodide (later), especially as he has syphilis; measures for overcoming infection (vitamins).
- (3) *For the emaciation*: After the circulatory and respiratory symptoms have come under control, the patient should be

FIG. 2



Photograph of the dorsal surfaces of the hands of the patient Robert M.X. The watch-glass shaped finger nails and the swollen tips of the ends of the fingers (acropachia) are well shown.

FIG. 3



Roentgenograms of the hands of the patient Robert M.X. The swelling of the soft parts of the finger-tips (acropachia) is well shown, but there is no marked tufting of the terminal phalanges, and only very slight evidence of periosteal thickenings in the phalanges.

FIG. 4



Roentgenogram of the chest of the patient Robert M.X.

made to gain weight (diet; rest; perhaps, also, insulin injections (fifteen units) one-half hour before each of the two principal meals).

Subsequent Note.—The Resident Physician, Dr. Marshall N. Fulton, sent me, in June, notes upon the results of certain other tests, the further course, and the termination.

On *bronchoscopy*, a large amount of pus could be seen, welling up from the right lower bronchus. *Roentgenograms after lipiodol injection of the bronchi* revealed no signs of saccular bronchiectases.

The patient continued to have intermittent fever, the evening temperature gradually rising to 103°. The pulse rate became ever more accelerated and the respiratory rate gradually rose to thirty-five per minute. The leukocytosis increased to a count of 22,700. The patient steadily lost weight.

On May 14, a soft, fluctuant swelling appeared on the anterior wall of the chest, just below the right nipple. An exploratory needle was inserted, and foul-smelling, greenish-yellow pus was obtained, cultures from which were negative (at the end of seventy-two hours). As the swelling rapidly increased in size during the next two days; the patient was transferred to the Surgical Wards. The swelling was incised (under novocain anesthesia) and the bloody pus evacuated. This pus had an odor like that of the patient's breath during preceding weeks. On opening the pleural cavity, similar pus was evacuated, and drainage was provided for by rubber catheter. On May 18, pus was obtained from the right lower back on paracentesis. Two days later, the patient died.

At *autopsy*, the pleural cavities were found obliterated by chronic adhesive pleuritis, except for a small area at the apex of the left lung and for two empyema cavities at the right base, the anterior of these communicating with the subcutaneous tissue of the chest-wall, the posterior containing 200 cubic centimeters of foul, greenish-yellow, purulent fluid. The pericardial cavity was normal. The aortic orifice was stenosed and a large calcified plaque projected from the valve. The mitral orifice was both stenosed and insufficient. The orifice of one coronary artery was narrowed, but there were no infarctions or necroses demonstrable in the heart muscle. The aorta

showed no signs of luetic involvement, but there were evidences of beginning aortic atherosclerosis (slightly elevated yellow patches).

Both lungs were covered by thickened pleura with widespread obliterations of both pleural cavities. Right middle and right lower lobes were collapsed, of a dark red color, and non-crepitant. The right upper lobe, though crepitant, contained bronchopneumonic patches. There was diffuse dilatation of the bronchioles of the right lung and there were gangrenous areas on the surface of this lung. The bronchi of the lower left lung were widely dilated, filled with pus, and surrounded by bronchopneumonic areas. Otherwise, except for mild nephrosclerotic changes, the autopsy findings were negative.

PSEUDO-ICTERUS DUE TO CAROTINODERMA FOLLOWING EXCESSIVE INGESTION OF CARROTS OF MANY YEARS' DURATION IN A PATIENT WITH CHRONIC ARTERIAL HYPERTENSION

Though pigmentation from eating carrots was first observed many years ago, the relatively frequent occurrence of carotinemia and carotinoderma has attracted the general attention of physicians in this country only recently. The patient before us this morning exhibits a carotin pigmentation of the skin, which has been present for several years; the patient himself and his physicians had believed that he was jaundiced. I shall ask Doctor Diack to give us the history of the case.

CLINICAL HISTORY (SUMMARIZED BY DR. S. L. DIACK)

This patient, Isaac R., a forty-nine-year-old Russian-Jewish insurance salesman, entered the hospital (Ward F-Main), for the first time, with *two complaints*: (1) "jaundice" and (2) high blood-pressure of seven years' duration.

Family History.—Nothing relevant to the patient's illness.

Present Illness.—Eight years ago, during the course of an insurance examination, he was told that he had high blood-pressure and that he should go on a high vegetable diet. From then until now, he has eaten no red meat and has cut down his salt-intake. His diet has consisted almost entirely of fresh vegetables and fruits. Carrots have been a staple article of his diet and he states that he has eaten them, on an average, twice every day for the past eight years.

Seven years ago, after a cold, he vomited for a day or so and, finally, fainted. His local physician examined him and told him that he had "jaundice";

he is positive that, at that time, his eyes as well as his skin were yellow. The discoloration of the eyes cleared up in four or five days, but the discoloration of the skin has grown gradually darker from that time on. He has noticed that the yellowish tinge to his skin has been most marked over the feet, hands, neck and face, but he states that his sclerae have never been discolored since the initial attack of "jaundice" seven years ago. At no time during the present illness has the patient noticed any dark urine, nor has he had any clay-colored stools. There is no history of colic or of any abdominal distress.

Physical Examination.—Well-nourished. Apparently quite nervous over present condition. Skin of hands and feet of a peculiar orange-yellow hue, with some darker pinkish irregular mottling; skin of trunk and upper legs only slightly discolored; face shows some discoloration, but much less marked than that of hands and feet; no excoriations; no pruritus. Sclerae and mucous membranes not discolored.

Chest somewhat emphysematous. Heart normal. Mild degree of arteriosclerosis of peripheral vessels. Blood-pressure 176 systolic, 96 diastolic. Liver edge just palpable (soft; smooth) one finger's breadth below right costal margin; upper level of liver dullness in fifth interspace in midclavicular line. Reflexes, sensorium, rectum and genitalia negative.

Laboratory Tests.—*Blood.*—Red-cell count, 4,750,000; hemoglobin, 85 per cent.; white-cell count, 7,400. Differential count: 69 per cent. polymorphonuclears, 27 per cent. lymphocytes, 1 per cent. large mononuclears and 3 per cent. eosinophiles. Size and shape of red cells and platelets normal. Icteric index of blood serum, 40. Van den Bergh test yields a direct delayed reaction. Quantitatively, the bilirubin content of the serum is 0.2 milligram per 100 cubic centimeters, the normal being 0.1 to 0.35 milligram per cent. Serologic tests: negative Wassermann, negative Hinton and negative Modified Hinton.

Urine.—Specific gravity constantly low; trace of albumin on one occasion.

Basal Metabolic Rate.—Normal.

Roentgenograms.—Films of gall-bladder region (after dye), negative. Films of teeth reveal slight absorption around roots of right lower first molar.

Course in Hospital.—During his stay in the hospital, he has had no fever; and pulse and respiration have remained normal.

Biopsy of the skin was refused by the patient, but parings off the corns of his feet showed a yellowish discoloration. Pathologic sections have not yet been studied. At no time during his stay could any traces of pigment be found on the night clothes, even when he was sweating freely.

Patient was discharged from the hospital with the diagnosis of arterial hypertension, carotinemia with carotin pigmentation of the skin, and anxiety neurosis.

DISCUSSION ON THE CASE

Here we have a man, past middle life, who believes that he has been "jaundiced" for seven years, especially as a diagnosis of jaundice was made by his physician. It is possible that there really was some jaundice at the beginning, since the patient feels sure that, at first, his eyeballs were yellow, as well as his skin. He tells

us, however, that the yellow color disappeared from the eyeballs at the end of a few days, though the yellow discoloration of the skin has persisted and has increased ever since.

You have learned from Doctor Diack that there is no bile in the urine, that the bilirubin content of the blood serum is within normal limits and that fragility tests are normal. This proves that the yellowish color of the skin is not due to bile-pigment; the patient has no true jaundice (either hepatogenous or hematogenous), but he exhibits what is known as "pseudo-icterus," or "false jaundice."

On inquiry, members of the Resident Staff learned that this patient, because of his arterial hypertension, has for the past eight years lived chiefly upon vegetables and fruits and that he has eaten large quantities of carrots—usually at two meals each day! When I asked him, just now, why he had eaten so many carrots, he replied that his wife "cannot cook anything else so well." I suspect that he is very fond of carrots and has urged his wife to supply him freely with them!

Professor Christian has called your attention to the fact that this pigmentation frequently appears in the skin of diabetic patients when they are kept long on a vegetable diet (*xanthosis diabetica*); as he has also told you, if some of the skin be excised and extracted with certain solvents, a comparison of the fluid obtained will doubtless show the identity of the pigment here with that which can be obtained from carrots by similar extraction. We know now that this pigment is carotin and that, in such pigmented patients, there is both carotinoderma and carotinemia.

A very careful study of the carotin pigmentations has been made by the physiologic chemists, Palmer and Eckles (*cf. J. Physiol. Chem.*, vol. 17, pp. 191, 211, 223, 237, 245, Baltimore, 1914), in plants, milk fat, body fat, corpus luteum, and blood serum, and they have discussed fully the relations of the hydrocarbon, known as "carotin," to the pigment in carrots and to the yellow vegetable pigments that accompany chlorophyll in all green plants. It is carotin that gives the yellow color to butter and to cream.

As early as twenty-nine years ago, von Noorden pointed out the xanthosis that occurs in diabetics on vegetable diets, and, later, Hymans van den Bergh and Snapper (and also Umber) suggested

the identity of the pigment of xanthosis with that of carrots. Moro, in 1908, had commented upon the yellow discoloration of the skin of infants fed upon carrot soup and had ascribed it to the pigment "carotin."*

In the early months of 1919, several German observers (Kaupe, Stoeltzner, Klose, and Schüssler) called attention to the "pseudo-icterus" that was common among both children and adults, who, during the Great War, had lived largely upon vegetable diets. They warned against confusing this pigmentation of the skin with that of true jaundice, emphasized the peculiar orange-yellow tint, and pointed out that the absence of discoloration of the sclerae is an easy means of differentiation this condition from real icterus.

Toward the end of 1919, Hess and Myers, of New York, also gave a good description of the syndrome as observed in this country (cf. *J. A. M. A.*, vol. 73, pp. 1743-1745, Chicago, 1919), and expressed the opinion that the pigmentation had often been confused with a mild grade of jaundice, or regarded as due to some obscure metabolic disturbance. They also suggested that the yellow color of the urine may be due largely to carotin rather than, as had hitherto been supposed, to a bile-derivative ("urochrome"). Hess and Myers went further and demonstrated, in these cases of carotinoderma, the presence also of the pigment in the blood—an actual carotinemia.

It is interesting that foods rich in carotin include not only carrots themselves, but, also, oranges, spinach, lettuce, butter, cream, and egg-yolk.

Patients with carotin-pigmentation of the skin will soon lose the yellow color if kept on a diet that is low in carotin-content. It will be interesting to see if depigmentation can thus be produced in the patient before us.

Rabinowitch of Montreal thinks that carotinemia in diabetics is prone to be associated with a high cholesterol content of the blood and points to a less favorable prognosis than in cases without xanthochromia.

Recently, several articles have appeared calling attention to the

* See editorial in *J. A. M. A.*, vol. 74, pp. 32-33, Chicago, 1920.

possible relation of the anti-infective vitamin A to carotin. It is thought by some, now, that the former can be synthesized in the body from the latter and that carotin is the pro-vitamin of vitamin A. (Euler, 1928; Moore, 1929; Hume and Smedley Maclean, 1929; Green and Mellanby, 1930; and others). Wolff, Overhoff and Eckelen (of Utrecht) have found that only very little vitamin A occurs in plants, whereas in animal products it is often found along with carotin; liver and cod-liver oil contain vitamin A with very little carotin, but in egg-yolk and butter both are present in relatively large amounts (*cf. Deutsche med. Wchnschr.*, vol. 56, pp. 1428-1429, 1930).

Clinical Papers on Diseases of Heart and Blood

AORTIC STENOSIS WITH CALCIFICATION*

By HENRY A. CHRISTIAN, M.D.

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and
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THIS patient that I am presenting this afternoon illustrates a form of cardiac disease which is moderately infrequent in occurrence but characteristic enough in clinical course and physical examination to justify a correct diagnosis much more frequently than is made.

F.S.T., male, aged fifty-three, P.B.B.H. Medical Number 38546; admitted to the hospital February 24, 1931, complaining of shortness of breath and nervousness of five years' duration.

Occupation is that of a stationary engineer, the work being neither strenuous nor particularly taxing.

According to his account he had always enjoyed good health with exception of measles, mumps, whooping cough and scarlet fever as a child, as well as diphtheria at the age of twenty. The patient himself knew nothing of ever having had rheumatic fever, but his mother subsequently has told us that he had rheumatism at the age of twelve, that he was in bed for several weeks with involvement of the ankle joints, and that at that time and again at twenty, when he was ill with diphtheria, nothing was told her about his having any heart disease or having a heart murmur. The patient denies venereal disease.

P.I. For five years the patient has had some dyspnea from moderate exertion. This has never incapacitated him and would have passed unnoticed except for more recent difficulties in breathing. He says he is of a nervous temperament, is easily startled and gets excited quite readily.

Five months ago while out hunting he had a sudden attack of dyspnea which came on after considerable exertion. He was forced to sit down and for some twenty minutes had some difficulty in "getting enough air to fill his lungs". For the past three months he has noticed that he gets out of breath rather easily, so that he avoids hurrying while walking or avoids carrying even a light burden up a flight of stairs. Three weeks ago while sitting at home

* Notes on a clinic given at the Peter Bent Brigham Hospital, February 26, 1931.

reading, he suddenly had an attack of coughing followed by difficulty in getting his breath, which lasted for some two hours. A local physician was called and then told him that he had a leaky heart and advised treatment.

Two nights before admission to the hospital the patient had his usual evening meal and retired about nine o'clock. At about 1.00 A.M. he was awakened by a dull pain of a gripping nature localized over the lower portion of his sternum. This pain did not radiate to any other part of the body. He felt that he had indigestion and took some soda and ginger and hot water with relief. The pain was accompanied by rather profuse sweating and difficulty in getting enough breath. The attack lasted some three hours.

Physical examination shows a man apparently entirely comfortable in bed with nothing very abnormal in his general appearance. On palpation and percussion his heart is only very slightly enlarged, the right border of cardiac dullness not being outside the right sternal margin and the left border of cardiac dullness being ten and one-half centimeters from the mid-sternal line, just in the nipple line. Heart sounds are of moderate intensity, the first sound being obliterated by a loud, long systolic murmur heard all over the precordium, but which gets progressively louder toward the base and can be heard best in the aortic area where it is accompanied by a definite systolic thrill. There is also a short, blowing, less intense murmur heard at the base of the heart occupying the first third or half of diastole. The pulmonic second sound is heard faintly. The peripheral vessels are not sclerosed. The blood-pressure on admission was systolic 120, diastolic 65; subsequent observations, systolic 110 to 112 and diastolic 50 to 52. Lungs show slight dullness at both bases posteriorly with rather loud, crackling râles, especially on inspiration. There is nothing abnormal about the abdomen. The legs show slight pitting edema over the lower ends of both tibiae. Ophthalmoscopic examination shows nothing abnormal. Wassermann reaction is negative. Urine negative. Blood counts normal.

The important features in this case history are the sex, a male; the age, in the later period of life (fifty-three); the history of rheumatic fever many years ago, at the age of twelve; the usual history of a developing cardiac failure, breathlessness chiefly; in this particular patient, pain suggestive of coronary occlusion; a systolic murmur, loud, rough, most intense in the aortic area, accompanied by a thrill; a pulse of rather small size without quick rise and fall; blood-pressure readings of 110-120 systolic, 50-65 diastolic. These findings justify the diagnosis of aortic stenosis, with the probability of deposits of lime salts in the aortic cusps, for the findings are those most usually encountered in this form of cardiac disease.

It is very remarkable that males so strikingly predominate in patients with aortic stenosis of this type. In a group of fatal cases of this kind here on my service at the Peter Bent Brigham Hospital with the diagnosis confirmed by autopsy, fifteen of twenty-one were males; in the series of Cabot,¹ twenty-five of twenty-eight; in the

series of Margolis, Ziellessen and Barnes,² thirty-four of forty-two, or a total of seventy-four males in ninety-one reported cases. I know of no other cardiac lesion which occurs in so large a proportion in males and in females so small. No explanation of this sex difference seems available. These men, as I have seen them, are not of the group who have undergone an excessive strain of physical exertion; rather they have been the usual average type of male with a history of the average kinds of physical work including some men of distinctly sedentary habit. A study of the history of these patients shows nothing that suggests a cause for the fact that few women have developed this particular form of heart disease. Syphilis, which does occur more often in males but not with so great a preponderance over women as in this group of patients, certainly is not the cause of this form of aortic lesion. In appearance it is entirely different from the lesion of syphilis, and in only two of my series was there any evidence of syphilis at autopsy, and the Wassermann reactions were negative in eighteen out of twenty cases where tests were made. Rheumatic fever, which is the probable etiology (a definite history of rheumatic fever in early life was obtained in eleven of my twenty-one cases), certainly shows no great difference in sex incidence.

It is curious that symptoms from this form of cardiac failure appear as a rule quite late in life, though I have seen the lesion as early as twenty-five years of age. With rheumatic fever early in life, as usually is the case, the aortic valve is damaged, but many years elapse before cardiac insufficiency results. How sharp the contrast to the usual sequence of rheumatic damage to the mitral valve with ensuing stenosis in which decompensation symptoms come relatively early, or to rheumatic or syphilitic aortic insufficiency where the time interval between cause and symptoms is, as a rule, much less. That the lesion is almost solely causative of stenosis of the aortic valve, as shown at autopsy, must be an important factor. Furthermore, whatever has caused the aortic lesion has done but little damage to the heart muscle, so that it has been able by hypertrophy to overcome for long years the increasing burden of a narrowing aortic outlet without causing symptoms. This is indicated by the actual appearance of the aortic lesion, and by the fact that in

some of these patients the physical signs of the aortic lesion have been noted long prior to the development of any cardiac symptoms.

Though in some of the patients a diastolic murmur typical of aortic insufficiency is heard, the peripheral vascular signs indicate that the actual aortic leak is slight; the form of pulse and the observed pulse pressure level point to this. In fact, with these physical signs, as enumerated in an earlier paragraph, and lack of Corrigan type of pulse one should conclude, in the absence of mitral stenosis, that the aortic lesion predominatingly causes a stenosis and probably is of the calcification type, particularly if the patient is an elderly male. In this particular patient of today, I have ventured to predict calcification in the aortic valve and will ask Dr. Sosman to make an X-ray examination with this possibility in mind. Next week I will give you his report. In many of these patients the roentgenologist ought to be able to visualize the calcification, for often it is present in thick, dense masses.

March 5, 1931. Last week I discussed a patient on whom I made the diagnosis of aortic stenosis with probable calcification in the valves. Let me read you the report of the X-ray examination made by Dr. M. C. Sosman since that clinic.

A seven-foot film of the heart shows moderate cardiac enlargement, chiefly to the left. The aortic shadow is widened, apparently due to tortuosity. The oblique view shows no dilatation. The measurements are: Mr. 4.8, Ml. 11.0, G.V. 6.0, Int. dia. 29.0. Fluoroscopy showed multiple areas of calcification in the region of the aortic valve, which moved toward the apex of the heart with systole and away from it in diastole, the total excursion being about 0.5 centimeter. The beat was regular and of good quality, not exaggerated as in aortic insufficiency.

As you will see, the roentgenologist has confirmed my prediction of calcification in the region of the aortic cusps and justified the clinical diagnosis of aortic stenosis with calcification.

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THE RELATION OF ACUTE RHEUMATIC FEVER TO CARDIAC DISEASE

By HARLOW BROOKS*

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FELLOW STUDENTS OF THE UNIVERSITY OF MICHIGAN:

I am embarrassed that I must begin a talk before my colleagues of my own University today with an apology. I had prepared a paper to present to you which represented some considerable study and thought. I learned just ten days ago that I was expected to speak on quite another subject. I could not seize the time to properly prepare another paper, such as I should like to give here on so grand an occasion, and I had almost decided to deliver my original paper, though it was out of key with the motif of your general subject. That would, however, have been very discourteous to our hosts and out of place on your program. Besides, the subject selected for me is so very fascinating, so important and also one in which I have been particularly concerned on my services at Bellevue Hospital during the past months, so I could not refrain from doing my best with it, even in this impromptu manner.

I have, therefore, elected to speak to you from my own experience. I have not opened a book nor read a paper on the subject in my preparation, but may I add that nearly 20 per cent. of the cases on my service during the past seven months have been instances of rheumatism, acute or subacute. Our admission rate on the Fourth Medical Service during these months has been over 400 new patients per month. I have, therefore, seen some cases of the subject on which I am directed to speak and you must try to pardon my frequent first person singular, and that I speak to you more as the clinician than as a University man.

* Given before the Alumni of the School of Medicine, University of Michigan, at Ann Arbor, June 18, 1931.

That acute rheumatic fever bears a close relationship to cardiac disease has been very long recognized in medicine. We have but recently, however, come to fully appreciate just how close this relationship is. Perhaps we of this day are altogether too prone to assume that all cardiac diseases, not otherwise accounted for in an etiologic way, is rheumatic. This is certainly going too far and yet it is the standpoint adopted by many workers today in the special field of cardiology. Not being a cardiologist, but an internist, I may be pardoned, perhaps, for dissenting considerably from this all too sweeping conclusion.

Nonetheless, lacking a really satisfactory classification of the arthritides, and still being unable satisfactorily to define acute rheumatic fever, to differentiate it from all other infections associated with the production of arthritis, cardiac involvement and inflammatory processes of the serous membranes, we must admit that the association of cardiac disease with rheumatism is an exceedingly frequent one.

One is justified today in making the statement that at least from 80 to 90 per cent. of cases of typical acute rheumatic fever are associated with definite evidences of cardiac disease. Swift and others would place the occurrence even higher, but pure clinicians are, as a class, rather loath to accept as definite proof of heart disease some of the evidences which are cited by Swift as diagnostic of cardiac invasion.

Certainly we are warranted, however, in saying that today most cases of typical acute rheumatic fever do cause cardiac disease of greater or lesser degree, just as we have admitted that cardiac involvement in the closely allied conditions of chorea is almost universal. It is certainly fair to admit that one may justly assume the heart to be diseased in rheumatic fever until the contrary has been proven to be the case.

When does cardiac disease take place in the course of acute rheumatic fever? In the answer to this question we have much changed in general opinion in the recent months or years. In the first place, we now fully recognize that the clinical picture of acute rheumatic fever varies greatly in different localities and especially under different climatic conditions. Thus the occurrence and the type of rheumatic fever prevalent in Montreal or London is quite different

from that seen in New Orleans or even in Baltimore or Washington. In the tropics, this disease is relatively rare and when it does occur it is in a vastly different form. For example, in the tropics, and even in New Orleans, so we are told, arthritic manifestations are very much in abeyance and the disease shows an altogether less aggressive front than that to which we practicing farther north are accustomed.

Thus it happens that especially in the South and even in New Orleans cardiac involvement is found among the very early manifestations of rheumatic fever, even entirely without arthritis. All of us in the North find that cardiac disease, pericarditis, endocarditis and notably myocarditis develop with considerable frequency after relatively mild introductory symptoms of a nasopharyngitis. Many of these cases in my observation subsequently mature quite characteristic evidences of being acute rheumatic fever. Thus it occasionally happens that cardiac disease may appear as one of the earliest recognizable evidences of acute rheumatic fever.

Most commonly, however, cardiac disease becomes recognizable in the aggressive phases of the arthritis and usually as either a pericarditis or an endocarditis. Probably myocardial invasion is quite as frequent but it is recognized with less positiveness due to its less striking signs. Frequently muscle disease is only suspected from an abnormally active tachycardia, by arrhythmias, sometimes by fall in pulse pressure, and occasionally by changes in the electrocardiogram only.

Every clinician knows that cardiac disease of any form is frequently not recognized in acute rheumatic fever until well into the period of convalescence. For this reason all of us are now requiring a much longer period of convalescence in rheumatic fever before we discharge our cases, and especially before we allow our patients to return to work and the usual habits and customs of life. It is all too frequent that we have found our patients returning to the office at the end of their convalescence with well-developed cardiac disease, appearing long after the arthritis has entirely subsided, the anemia disappeared and the temperature fallen to normal.

Even after the stage of full convalescence, one may find cardiac lesions becoming apparent from acute rheumatic fever. This is particularly strikingly seen in office practice. Often months after

a patient has returned to his work and full life obligations, he reports to the office with a very definite cardiac lesion which has appeared after every vestige of the original infection has long gone.

There is still another period after acute rheumatic fever which may declare itself by the discovery, perhaps, of a very grave cardiac defect, heretofore entirely unsuspected. I am accustomed to speak of these cases as latent cardiac rheumatism. It is seen in cases of recovered rheumatic disease which have long since been discharged as entirely free from cardiac disease. These patients stand the usual stress of life perfectly well but when they are submitted to some unusual stress—they join the football squad or are transferred to the artillery where the work is heavy and exhausting—then only does a cardiac hypertrophy develop. The patient is found to have developed an “athlete’s heart” or sometimes a sudden and unheralded decompensation takes place and at the autopsy we find a myocardium the seat of an old fibrotic process which we can almost certainly trace back to a perhaps long-forgotten attack of rheumatism.

Thus it seems that one can almost never say that the heart in any case has fully escaped the effects of rheumatic invasion. The very important thing for us clinicians to recall is the ubiquity of the process, its often slight signs and symptoms and to therefore more carefully supervise, particularly the convalescent phases of rheumatic fever, especially when our patient returns to his ordinary habits of life.

For myself, and I think for most other clinicians, it is as impossible to study any clinical problem without an appeal to the basic pathology as it is for a musician to perform without first knowing the mechanism and range of the instrument on which he is to play. Let us for a few moments review the more essential pathology of the heart in rheumatic fever. It is only with such a basis of knowledge that we can intelligently go on to the discussion of treatment and prevention.

The rheumatic poison in the tissues of the heart acts almost certainly in but a few different ways. Probably the earliest changes occur in the heart muscle fibers, and this change is particularly likely to occur in cases which manifest a high fever and marked prostration—what we speak of clinically as a high grade of toxemia. The muscle cells undergo a parenchymatous degeneration, very sim-

ilar to that which takes place in diphtheria. Such a diseased fiber or cell may then disintegrate, perhaps be transformed over into a type of fatty degeneration, so-called, or in young and otherwise healthy subjects it may recoup and build itself up again into a tolerably normal fiber. If, on the other hand, the cell breaks down and disintegrates, its blank space is filled in the adult or in old age not by a new-formed fiber, but by a replacement process with fibrous tissue, inert and useless in so far as cardiac function is concerned. This establishes a break in the continuity of muscle conduction which is so very important in the function of the heart.

Areas of small round-cell infiltration take place about the arterioles in the cardiac interstitium. They impede the circulation, nourishment and oxygenation of the muscle cells, favor their degeneration and again set up a perivascular production of fibrous connective tissue.

Probably closely allied to this process of small round-cell infiltration in the interstitium is the formation of the specific lesion of acute rheumatic fever, the hall-mark, as it were, of the disease, the Ashoff body. These may form wherever connective tissue is present, in the pericardium, the interstitium of the muscle and even in the framework of the valves themselves. Wherever they form, they are probably permanent and in so far as we know they never resorb and disappear but they always remain as an irritant foreign body, eventually to be encapsulated in favorable instances by a shell of fibrous connective tissue.

The connective tissue scars thus formed, as you see in any of the histologic foci of rheumatic disease, in their process of healing contract, as all connective tissue does when it becomes old and of the adult type, it cicatrizes with again the production of a foreign body, one which cuts off blood-supply through the arterioles and capillaries, dams back the circulation in the veins and impedes the functions of conduction, irritability and contraction, necessarily inherent in normal muscle function. In the majority of instances, then, the lesions produced by the rheumatic virus, whatever it may be, are permanently damaging in character, thus bearing out the well-recognized clinical fact that the rheumatic heart never returns to full normalcy.

The most primitive division of the structures of the heart ana-

tomically is into the pericardium, the myocardium and the endocardium. All of these structures are affected in the manner above described in acute rheumatic fever. It is usually easy to recognize an endocarditis when it occurs on one of the valve segments or attachments, but it is a very difficult matter to recognize an endocarditis when it is the mural endocardium alone which is affected. Pericardial involvement is also not so difficult to recognize clinically when the membrane of the anterior aspects of the heart is chiefly invaded, but when it is the posterior plane which is mostly involved or when the process is not largely fibrinous, or when one does not chance to examine the heart at a time before much secretion of fluid has taken place to hide the characteristic creak or rub, it is indeed easy to fail to recognize a pericarditis. Most of us do fail to recognize this exceedingly striking lesion unless we are constantly on the lookout for its appearance in these cases of acute rheumatic fever.

When the endocardium is involved, we are often able to definitely locate the point of the valvular lesion from the knowledge of the characteristic physical signs, especially detailed by Lannec and later most beautifully by the elder Austin Flint. Now in rheumatic fever we have long known that the most frequent valvular lesion is of the mitral segments, next of the aortic ring and segments, then of the tricuspid, and lastly of the pulmonary valves. It is by no means infrequent that all or nearly all of these segments are diseased, but also how very difficult indeed it is to estimate the location or even the mere occurrence of a mural endocarditis!

Most difficult of all to recognize, probably most common of all to occur and certainly most important of all as measured by the permanency and seriousness of heart damage, is a rheumatic myocarditis or myocardial degeneration. In some cases, the process is obviously an acute inflammatory one; in other instances it is more primarily degenerative in type with secondary fibrosis and cicatrization. Arrhythmias, fall in pulse pressure, decreased voltage and other electrocardiographic evidences are the signs on which we must rely in large part for the diagnosis of a myocarditis or a myocardial degeneration of this form.

Pancarditis, involvement of all these structures, is seen all too frequently in rheumatic fever, either in its acute phases or perhaps

years later when only the circulatory break may have become evident, and manifest clinically with the signs of cardiac decompensation.

As I have already intimated, the recognition of cardiac involvement in rheumatic fever depends largely on the recognition of the signs of these various pathologic changes which I have rapidly detailed. There are, however, other signs and some symptoms which indicate cardiac invasion in acute rheumatic fever. It is unhappily true that most of these additional signs and symptoms may occur independently of cardiac lesions or from some other complication, but when they appear, one is invariably stimulated to a more meticulous examination of the heart for the more specific signs evidencing the pathology which we have so briefly considered.

One of the most striking and diagnostic of these symptoms is pain. This pain is usually located in the precordium and it is accompanied by a sense of weight and oppression, sometimes by a degree of cyanosis. This pain is most striking in pericarditis, but it occurs also in myocarditis and in endocarditis sometimes independently. Local tenderness over the heart as demonstrated by heavy percussion, in the attempt to outline the cardiac or mediastinal borders, is also occasionally present. Definite dyspnea may occur in cardiac involvement, sometimes with even very little signs in the heart area itself.

Occasionally, a chill ushers in the cardiac invasion, but this is not so common as is an elevation of the temperature, over and above the peak formerly present. Almost always there is an increase in the cardiac rate and arrhythmias are other very striking suggestive signs, especially when the muscle is seriously involved. Where the involvement is of the mural endocardium or of the muscle, modification in the quality of the heart muscle tone is often very striking and significant. In such instances, of course, the electrocardiograph affords information of a most valuable character, though it is very unwise in my experience to put too much confidence on electrocardiographic aberrations unless confirmed by clinical signs. In nearly all cases of cardiac involvement there is an increase in the polymorphonuclear leukocytes and in our wards this winter the characteristic "shift to the left" of the polymorphonuclears is manifest. Such evidence, even with the absence of definite cardiac signs, is

highly significant diagnostically, unless accounted for by other acute complications.

Pain, already noted, is another evidence of cardiac involvement which should never be underestimated. As a rule, it is most marked in cases in which the pericardium is involved but it occurs also in endocarditis and in myocarditis. The pain is usually of a dull, pressing character, rarely reflected wide from the precordium and rarely to be mistaken for an angina. Too much stress must not be placed on failure to detect typical signs of pericarditis. I think all of us who follow our cases from the ward to the deadhouse realize the difficulty of diagnosis of pericarditis. Only too frequently the characteristic rub may be present for but a very short time. It comes and it goes so that house and visiting staffs are always in dispute as to its presence or absence. It is an old medical aphorism regarding the diagnosis of pericarditis, especially in rheumatic fever, that if you think it is present, it is, even if you cannot be sure of it or be able to demonstrate it to others. A rather indistinctness of the heart sounds, and perhaps a diminution of the palpable apex pulsation are both highly diagnostic indications of its existence. Changes in the area of mediastinal dulness, when they can be made out with reasonable accuracy, are also very helpful and of course one always suspects a pericardial effusion when the sounds at the apex are distinct and indistinct and yet the pulse full and as before.

We are accustomed to rely a great deal on the use of the fluoroscope in our recognition of the cardiac complications in acute rheumatic fever. We push our patient's bed into the fluoroscope room which is just off our wards and with the patient turned to one side or sitting up in bed we are usually able to get evidence which to me is much more convincing in many cases than the X-ray plate and much more possible for those of us whose radiographic department is far from and all too detached from the clinical management of the case.

I have several times mentioned the value of the electrocardiograph in the recognition of cardiac involvement in acute rheumatic fever. Where wards are wired for electrocardiography, this is a very important thing to do when in doubt, or when the cardiac station can be utilized without too much stress for the patient, but it is a useless procedure where definite clinical signs are present

unless the record is made for the interest of the study and not to facilitate diagnosis. We shall, I think, all admit that at least during the active stages of the fever that almost without exception electrocardiographic modifications will be found in acute rheumatic fever, whether or not other evidences are present. Why not then assume, as we are justly entitled to do, that practically all cases of acute rheumatic fever have more or less cardiac defect as a result of the disease? Certainly such a hypothesis is justifiable.

We are still familiar with the characteristic flitting manner with which rheumatic fever invades the joints. As one articulation subsides, another is most likely to become involved. One wishes that this tendency also pertained as regards the involvement of the heart, but quite the contrary is the case, for when invasion of the heart takes place, be it of the pericardium, of the myocardium, or of the endocardium, the lesion remains at least for a very long time and postmortem one is commonly able to find these hall-marks of the disease years after in some stage of persistence or of cicatrization. True, one finds the symptoms of the lesion vary from time to time, the grade of the fever, the number of the leukocytes, the character of the endocardial murmur or the pericardial rub, but the acute lesion remains until long into convalescence. Unfortunately, especially as regards muscle invasion, one cannot well estimate the degree of damage effected by the signs and symptoms with any great certainty.

Every one of us has earnestly tried to discover some manner in which we might prevent heart involvement in this ubiquitous disease. Logically enough, rest in bed has been the method most advised and none of us can dispute its wisdom, not alone because of its possible effect on the heart, but also because rest is the one outstanding indication in the course of the entire disease. I cannot feel, however, from my observation, that rest, even when most punctiliously followed out, affects either the rate or degree of cardiac involvement, beneficial though it certainly is, in the conservation of the heart and in the limitation of the ultimate damage to the heart reserve.

We also well appreciate the effect of the salicylates when adequately given in rheumatic fever. When properly given and in sufficient dosage, preferably by rectum, one sees a remarkable diminution in pain not only in the articulations involved but also in the

physical appearance of the invaded joints. Heat and tenderness, redness and edema are all abated and one might justly expect that a similar improvement might take place in the tissues of the invaded heart, or that when given to its full pharmacologic effect that the drug should prevent the appearance of the cardiac lesion, as it certainly does prevent new joint invasion. Unhappily, I cannot believe that this takes place as regards the heart. From long and careful observation in many cases I am forced to the conclusion that the salicylates in no manner or degree prevent, nor do they apparently benefit cardiac involvement in acute rheumatic fever, nor do they materially reduce precordial pain as when caused by a pericarditis or the like. Fortunately, the same clinical studies have convinced us that when given in the maximum doses, which are most effective in the general disease, the drug does not depress or in any other way injure the heart. Fever is usually lessened, the patient feels better, but we do not materially help or prevent cardiac involvement. The question then arises quite naturally if we do not have in the agent which causes the heart complication some additional factor in the way of etiology which is not part of the primary cause of the disease. Time only will tell us.

Most of us have found, to our cost, that trauma inflicted on any joint in acute rheumatic fever acts as an incitor of involvement of that joint. Can we, by lowering the heart rate, by lessening cardiac work, in any way prevent heart invasion? One would like to answer this question, and, indeed, it does seem very logical to expect that by lessening the labor of the heart that we should in some way conserve it from the poison of the disease, but we have as yet no real evidence to prove it, though, as in all other similar diseases, we do attempt to slow down the heart and to lessen the obligatory service by applying ice bags to the precordium, by the use of febrifuges as pyramidon, phenacetin and the like. I cannot, however, see that we have as yet shown a corresponding benefit to the heart either in a curative or in a preventive way.

What is true of the salicylates in so far as mitigation or prevention of cardiac involvement in this disease is concerned is equally disappointing as regards the alkaline method of treatment of rheumatism, as we still occasionally use it. So also the iodides which are

often definitely beneficial in the convalescent stages of the disease especially seem without favorable effect here.

In former times, we were accustomed to put great stress on the dietetic treatment of rheumatism in the acute as well as in the chronic phases. I think that most of us now feel that this is, in the main, unnecessary and often very unwise, since as a result we tend to accentuate the profound anemia which is so important and sinister a feature of the disease. The heart cannot fail to suffer also from such a profound anemia, and it is now our custom to give as iron-rich a diet as the patient's digestive powers will tolerate. We also give iron throughout the course of the disease, usually in the form of Basham's mixture, of venerable and deserved reputation, or in some similar preparation. Do these measures prevent cardiac involvement or do they in any way benefit the cases when they have developed? I hope that they do, indeed, I almost believe that they do make for a better ultimate result since they should at least lessen the degree of degeneration in the all-important cardiac muscle.

We have, during the past term of service, given especially by mouth, sugar solutions freely in acute rheumatic fever, we believe with some good general effect, though it is, of course, quite impossible as yet to entirely evaluate such agents. One can at least greatly elevate the calory intake in cases which have difficulty in taking other nourishment in the disease by giving especially the sweetened fruit juices by mouth, lactose solutions by rectum and in a small group of cases with certain heart defect we have given concentrated sugar solutions intravenously, certainly not with bad result, and possibly with some benefit.

Most of us have been experimenting recently, I cannot call it a more positive term, with vaccines in the treatment of subacute and chronic arthritis. You are well aware that several investigators of irreproachable honesty and sincerity have been isolating organisms of one kind or another either from the involved tissues or from the blood in rheumatism. Is this a permissible or advisable thing in so far as cardiac involvement is concerned in cases of acute rheumatic fever with consequent heart defects? My own observations in this respect are limited, but I have seen the effects in the services of my colleagues and I see nothing of value in the method in so far as the heart is concerned at least either in acute or in chronic cardiac

lesions caused by rheumatism. I must as yet advise against the method.

Most of us certainly feel that acute rheumatic fever is commonly introduced with a nasopharyngitis, a sinusitis, or, most frequent of all, by a tonsillitis. How radically should such initial lesions be treated in cases of cardiac involvement? There are many answers to this question. Shall dead or definitely infected teeth be removed in the height of the disease with or without demonstrable heart disease? There are many who feel that infected tonsils should be forthwith enucleated, infected or suspicious teeth promptly extracted and radical sinus operations are undertaken by a few hardly souls.

My own experience and my observation of others have convinced me that such practice is not only useless but also highly dangerous and especially so in cases in which the heart is already in difficulties. I have seen a good many instances in which such measures have been apparently promptly followed by chill, marked rise in fever, high leukocytosis, prostration, cardiac invasion of a particularly violent character and not infrequently by pulmonary, splenic and renal infarction. I think that it is a very dangerous thing to do, but some excellent physicians, I must admit, have been fortunate in not having such definitely bad results as I have observed.

Of course, I do not for a moment mean to infer that a tonsillar or peritonsillar abscess should not be opened, that a sinus should not be drained or that obvious pus should not be evacuated when it is surgically indicated, but I am certain that only the more mild methods should be employed to effect this end, and no unnecessary opening up of new lymphatic spaces should be permitted. I am particularly bitter against dental operations, in these cases, especially the removal of otherwise sound teeth and the curetting of the root cavity.

Foreign proteins are also in my observation dangerous agents to employ in cases in which active cardiac defects are found, and beneficial as they certainly are in a limited number of cases of chronic arthritis, they should not be employed as long as the heart defect furnishes an important figure in our anxiety.

Another question of importance which constantly arises in our management of cases of cardiac involvement in acute rheumatic fever is as to the use of digitalis, strophanthus and the like. That

depends. There are occasional cases in which acute dilation either threatens or occurs and in such any competent clinician will resort to these drugs and frequently in maximum doses. We all recognize that in cardiac disease of this character the effects of these drugs are far less potent than in hearts with relatively normal muscle. We must use them occasionally and in emergency frequently, but in the general run of cases in which no immediate danger of cardiac failure apparently impends, I believe they should be omitted. We must rely in the ordinary instance on rest and time as our only real curative agents of the cardiac defect. We must not, however, stand idly by and allow dilatation to take place, but one must treat the problem precisely as he would such a heart in any other condition.

Elimination must be well maintained throughout. One of our most valuable drugs to this end is water, given abundantly. Usually the mildly alkaline waters are best employed and with the water such laxatives, preferably of the saline characters, are useful with or without heart lesions. Symptomatic treatment must be practiced throughout, and our constant object should be to give the patient as much comfort and rest as possible. Anything which exhausts our patient, which causes him pain and discomfort, is particularly bad for the patient who has an additional cardiac defect. Sedatives are to be used as necessary to insure sleep. The brilliant analgesic effect of the salicylates is to be employed constantly and with adjuvants of the more powerful sedatives and analgesics when necessary. The patient with rheumatic fever and a crippled heart is to be treated, not the disease, of which we know very little.

When a cardiac defect is known to have taken place in any case of acute rheumatic fever, the convalescence of that case must always be prolonged until the physician is fully convinced by cautious experiment that the patient is ready to get up, about and cautiously back to his business and social responsibilities. We must never forget the great frequency with which grave cardiac lesions become apparent long after the acute process has subsided and we should insist that all convalescent patients report back, especially for cardiac examination at rather frequent intervals for at least one year after the patient has left his bed.

He who has suffered from such a lesion must without fail be certain that he does not overexert either in work or sport, that he

secures abundant sleep, relaxation and rest and that his anemia is corrected by an adequate and suitable diet.

Particular care must be exercised as to young children and after it has been possible to estimate fairly the degree of permanent crippling that he has suffered the parents and the child himself should be specially directed in the selection of his occupation, his sports and as to his necessary habits of life. Undoubtedly, we physicians have taken this responsibility too lightly in the past and it is all too frequent that we find old rheumatic hearts in our football squads, in the crew and pathetically common we find that young men and women are allowed to select and prepare themselves for occupations in which, from the nature of their old rheumatic hearts, it can never be possible for them to succeed.

We all know how susceptible rheumatics are to subsequent attacks of the disease and we know also how almost inevitably when this takes place that the heart once involved by the rheumatic virus succumbs to other attacks. We know, also, that these hearts are very prone to develop subacute bacterial endocarditis. Indeed, most of us feel that a good many of the latter attacks of rheumatism originate from the old cardiac focus itself.

It is, therefore, particularly important that when the acute rheumatism and its cardiac picture have subsided that we carefully appraise the whole patient and direct him how to prevent recurrence of rheumatism, to take the salicylates at its earliest symptom, to secure adequate rest, to protect himself from the conditions which we know to be concerned in the predisposition to the disease and when a habit of recurrence appears to portend, climatic adjustments should be also made, if possible.

Now is the time to remove suspected tonsils, to treat infected sinuses and even to yield to the popular sport of dental extraction, but only when some definite lesion can be shown to be present.

The prognosis in heart disease which has originated in the course of acute rheumatic fever depends on a great many factors: on the character and degree of the lesion, on the stress which the injured heart must meet, on the subsequent habits of life, on occupation, climate, especially on the recurrence or absence of other attacks of rheumatic fever and in no inconsiderable part on the doctor who is responsible for the management of any phase of the case from the initial disease to old age.

BUNDLE-BRANCH BLOCK

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It is encouraging to note the increasing interest in the study of bundle-branch, or intraventricular, block. This condition, though comparatively common, received scant attention in the earlier years of investigation of the disorders of the mechanism of the heart-beat. Caused by a block of the impulse in one of the two main branches of the bundle of His, it is one of the characteristic findings in the senile heart and one of the more rare manifestations of rheumatic or syphilitic heart-disease.

Without much difficulty, I have been able to see fifty cases of this condition during the past four years; most of these were found in the wards and out-patient department of the Johns Hopkins Hospital, some at the Union Memorial Hospital and in practice.* These patients were residents in Maryland and adjacent states, except one who lived in North Carolina. The group may be considered, therefore, to present a typical picture of bundle-branch block as it is seen in the Middle Atlantic States.

Etiology.—The fifty cases of intraventricular block may be grouped from the standpoint of etiology as follows:

	<i>Arteriosclerotic</i>	<i>Rheumatic</i>	<i>Syphilitic</i>	<i>Total</i>
No. of Cases.....	43.....	3.....	4.....	50
Per cent.	86.....	6.....	8.....	100

The Wassermann reaction was not noted in three cases classed with the arteriosclerotic group. The average age of these three patients was 57.7 years. Also included in this group are two cases with positive blood Wassermann reactions; the blood-pressure in these two cases was, respectively, 204/100 and 240/130, and they were considered to be instances of hypertensive cardiovascular disease with

* I am indebted to Drs. W. S. Thayer and B. H. Rutledge, W. S. Love, Jr., J. L. Dorsey and to Drs. S. R. Miller and F. W. Gluck for permission to see patients under their care and to include them in this series of fifty cases.

arteriosclerosis, with syphilis playing possibly a subordinate part in the picture.

Of the rheumatic group there is little doubt: one, a man of fifty, gave a history of tonsillitis and rheumatic arthritis, showed aortic insufficiency and a negative Wassermann reaction; a woman of the same age had had much tonsillitis, had had acute rheumatic polyarthritis shortly before being seen and had a typical chronic rheumatic endocarditis; the third patient, a woman of forty, gave a history of much tonsillitis and of rheumatic fever: though the Wassermann reaction of her blood was doubtful she showed a typical rheumatic endocarditis.

One case classed as of syphilitic etiology was that of a man of fifty-eight who showed a positive Wassermann reaction and aortic insufficiency; he was thought to have a syphilitic aortitis and myocarditis. His blood-pressure was 145/50. A second patient, a negro of forty-one, had had rheumatic fever and showed a negative blood Wassermann reaction; he had aortic insufficiency and a marked myocardial weakness and in spite of certain doubtful features he was thought to have syphilitic aortitis and myocarditis. The third case was that of a negro of forty with a positive Wassermann reaction in the blood and without a valvular disease; he was thought to have syphilitic myocarditis. The fourth case was that of a white man of sixty-nine, with history of chancre twenty-seven years before. He showed a positive blood Wassermann reaction and, in addition to intraventricular block, had a complete auriculo-ventricular block.

Age.—Thus, the average age of patients with bundle-branch block in which syphilis was thought to play a part was fifty-two years. The average age in the rheumatic group was 46.7 years. Of the remaining forty-three patients thought to have intraventricular block as the result of atheromatous degenerative changes in the heart the average age was found to be 59.7 years.

Sex.—Hill found bundle-branch block in thirty-one males and in ten females, the percentage of the females in the series being 24.4. In our group the sexes were represented as follows:

	<i>Cases</i>	<i>Per Cent.</i>
Male	37.....	74
Female	13.....	26
Total	50.	100

Symptoms.—Of the fifty patients with intraventricular block, forty-three complained of dyspnea. Thirty-three showed orthopnea and thirty edema during at least a part of the period of observation. Pleural effusion was found in four cases and ascites in five. At least thirty patients showed definite cyanosis.

Cardiac Signs.—The physical signs of the same fifty cases have recently been reported by King and McEachern.* In a majority of cases a reduplication, or quick repetition, of the apex thrust may be seen or felt, or both seen and felt. The first heart sound may be split into two elements, or there may be a single first sound followed after an appreciable interval by a systolic murmur, or two separate murmurs may be heard. It is not uncommon, however, to find a clear first heart sound, sometimes in the presence of a distinct reduplication of the apex thrust.

The quality of the heart sounds in thirty-one cases in which a specific note was made of this feature was as follows: "strong" in four, "normal" in four, "weak" in twenty-three. In some instances the heart sounds at the apex are quite inaudible.

Carter³ reported the first series of a considerable number of cases (twenty-two) in 1914; in his contribution certain electrocardiographic criteria were laid down as the basis for the diagnosis of bundle-branch block. Carter's standards have been used generally by subsequent observers as the minimum requirements in the diagnosis. One of these criteria, which is in accord with the original findings of Eppinger and Rothberger⁵ from experimental branch block in dogs, holds that progressive decrease in the height of the R-waves in the three leads of the electrocardiogram (the so-called "levogram," or left ventricular sequence) is an indication of right side block; conversely, a progressive increase in the R-waves has been considered generally to represent the "dextrogram" and to be due to block in the left branch of the His bundle. Recently, Barker, McLeod, Alexander and Wilson² have challenged this concept and think that the picture heretofore considered to represent the "levogram" or "left ventricular preponderance" is in reality the "dextrogram," and *vice versa*. I am not prepared to enter this discussion

* The Nature of the Physical Signs of Bundle-Branch Block, J. T. King and Donald McEachern. Read at the meeting of the Association of American Physicians, May 5, 1931. In press, *American Journal of the Medical Sciences*.

but wish to point out that the diagnosis of right side block in our series was made when the tracing showed, together with the other accepted criteria, progressive decrease of the R-waves, while progressive increase of the R-waves has been considered to indicate left side block. On this basis, the site of block in our fifty cases may be indicated as follows:

	Number	Per Cent.
Right Side	47	94
Left Side	2	4
Doubtful	1	2
Total	50	100

There seems to be no radical dissension otherwise from the electrocardiographic standards of Carter, although Luten and Grove⁷ have described recently what they believe to be early evidences of intraventricular block—changes in the electrocardiogram that fulfill only part of the generally accepted criteria.

Blood-pressure.—Excluding three instances in which there was also A-V dissociation with idioventricular rhythm, King and McEachern found systolic pressures of 170 millimeters mercury or above in seventeen of fifty cases; and of 200 millimeters mercury or above in five instances.

Atheroma.—Evidences of arteriosclerosis in parts of the body outside the heart were the rule. In forty-two cases a definite note of arteriosclerotic changes was made, in three the condition of the vessels was not recorded.

Prognosis.—Bach¹ studied the prognosis in his series of eighty cases by considering the etiology. Among fifty cases thought to be caused by cardiac degenerative changes ten patients died after the lapse of an average period of 0.3 year; one had lived, at the time of the report, fourteen years and one nine years. Bach gives a fairly good prognosis for this type of disease.

Of my patients in whom arteriosclerosis was thought to provide the etiology for bundle-branch block, thirty-one have been traced; eleven (35.5 per cent.) are living after an average period of one year and six months, and two of this group have been living for four years from the time of the first electrocardiographic diagnosis. Twenty (64.5 per cent.) are known to be dead; sixteen of these died after an average period of 11.6 months, while three died at a

time unknown, prior to the sending of the questionnaire; one died of accident one year after the discovery of the lesion. Thus the prognosis in this series is very bad, even in the arteriosclerotic group. Our figures in this group are similar to those reported by Hill.⁶

Reports from the syphilitic patients are unsatisfactory; three are not to be found and one died one year after the discovery of bundle-branch block.

Of the rheumatic group of three patients, one died at the end of eleven months from the finding of branch block, one died at the end of three months while one gives no report.

DISCUSSION

In our series, the etiologic factors most concerned in bundle-branch block are clearly age and arteriosclerosis. Eighty-six per cent. of the cases were apparently due to these causes. Of the four cases thought to exhibit cardiovascular syphilis and bundle block, two are open to doubt, since a negative blood Wassermann reaction was found in one while in the other case the syphilitic infection had been acquired twenty-seven years before intraventricular block was discovered at the age of sixty-nine. Of the four cases of supposedly syphilitic etiology, only one showed the typical picture of syphilitic aortitis and aortic insufficiency.

Thus, it is clear that syphilis is only rarely associated with intraventricular block in Baltimore. In Bach's series from London the proportion of syphilitic cases was considerably higher than in ours. This discrepancy cannot be due to dearth of cardiovascular syphilis in Baltimore where the large number of negroes, notably liable to this condition, affords only too many instances of luetic disease of aorta and heart. For example, Carter and Baker⁴ have shown that syphilis of the aorta occurred in 15.14 per cent. of all cases of heart-disease admitted to the Johns Hopkins Hospital in recent years. In other words, the incidence of cardiovascular syphilis seems to be about twice as great in the group of cardiac cases at large as it is in the group of cases of intraventricular block.

It seems reasonable to state that our series is especially valuable in showing the small liability of patients with syphilis of the cardio-

vascular system to bundle block. It does not appear from Bach's report just how the diagnosis of bundle-branch block due to syphilis was reached in his large number of cases listed in this category. Perhaps the London series is of especial value because of the larger incidence of rheumatic fever in the British Isles than in Baltimore and the relatively large proportion of cases of rheumatic heart-disease associated with bundle-branch block.

It would require careful analysis of many factors to deduce from our series to what degree the bundle block, as such, affected the prognosis and to what degree the obviously bad prognosis is due to other changes in the heart. In our arteriosclerotic group, approximately one-third of those who were traced were alive at the end of eighteen months from the discovery of the condition, while about two-thirds had died after the average lapse of 11.6 months after the first electrocardiogram. We must assume, therefore, either that bundle block itself is a condition that offers the gravest outlook or that the lesion occurs in hearts that are very seriously affected by degenerative changes. The duration of life in this group of arteriosclerotic cases of ours was shorter than that reported by Carter and Baker from Danglade's tables of cases of syphilitic aortitis with aortic insufficiency. These observers found the average expectancy of life in such cases to be from twenty to thirty-five months from the onset of the symptoms.

SUMMARY

It may be said, then, that the most typical example of bundle-branch block in Baltimore is that of a man of about sixty years, who shows evidences of generalized arteriosclerosis and in whom the systemic blood-pressure is as likely to be elevated as to be normal. Such an individual is dyspneic and edematous on admission to the hospital; electrocardiographic examination produces a tracing similar to that shown in the illustration. While he may show a temporary improvement, his cardiac symptoms persist and the expectancy of life is a year or two from the discovery of the lesion.

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HYPERTENSION *

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A STUDY of figures afforded by life insurance examinations show that hypertension is sufficiently frequent to warrant considerable thought. Although perhaps not as frequent in the young as has been suggested by some authors, it is encountered sufficiently often in the middle-aged and old. It is responsible for not only a great deal of inconvenience, but, is probably one of the most prolific causes of mortality in men past fifty. Frost's figures are interesting in this regard. He showed that out of 146,922 cases examined for life insurance, 2,568 cases showed a persistent increase of blood-pressure. This represents an incidence of approximately 1.74 per cent. This incidence tallies surprisingly closely with that given by Diehl and Sutherland. They examined 5,122 students and found 1.6 per cent. showing a persistent increase in blood-pressure. Nine to 16 per cent. of the total number examined showed an increased blood-pressure (over 140m. systolic) and on subsequent examination proved to belong either to the transient or intermittent group where the increased pressure was due to nervousness or excitement, or was secondary to some complicating disease. In Frost's series, out of the 2,568 cases of persistent hypertension observed, 75 per cent. belonged in the essential group 17 per cent. in a group associated with renal disease, 6 per cent. were transient, and 2 per cent. were associated with arteriosclerosis. It is thus evident from these figures that essential hypertension is fairly common, and leads very often to complications which may terminate life. To properly appreciate how impossible it is to generalize regarding the treatment of this disease, it might not be out of place to discuss briefly the clinical classification of this affection and some of the factors associated with its occurrence.

Clinically the French have classified hypertension into a benign type, moderately severe, and the very severe or malignant type.

* Presented before the Nevada State Medical Association September 27, 1930.

Others have classified it into the presclerotic, idiopathic, or essential hypertension (uncomplicated type), and the secondary group where it is associated with or due to other complicating diseases. However, according to Frost, even the benign group of essential hypertension show very early signs of cardiovascular disturbances, as evidenced by a rapid pulse, occasional heart murmurs, hypertrophy of the heart, or cardiac irregularities, susceptibility to mental or physical effort, which later on develop into the characteristic cardiac, renal or cerebral disease. The question of causal relationship between these complicating factors and the hypertension has been the subject of a great deal of discussion. One school, of which Moschkowitz is a leading exponent, leans to the opinion that hypertension is due to an increased peripheral resistance, brought about by a narrowing of the isthmus of the aorta, sclerosis of the peripheral arterioles or those of the viscera. The other school, initiated by Vaquez, *etc.*, contends that the hypertension is a functional reaction to some endogenous substance such as adrenalin, which causes a constriction of the peripheral arterioles and the consequent rise in blood-pressure. This theory finds some support in the recent observations gathered by Oppenheim and Fishberg, and Hajos and Labbé in France, concerning the relationship of tumors of the suprarenal gland to persistent hypertension. There is a third group exemplified by Major, and others who consider that the substance responsible for the increase in blood-pressure is one whose nature has not yet been determined, and that it is this agent which produces the vasoconstriction which leads to persistent hypertension and consequent arteriosclerosis. Richards and Schmidt have demonstrated the effect of adrenalin and pituitrin on the efferent arterioles of the kidney glomeruli with consequent local hypertension and albuminuria. This would explain the apparent kidney changes on a functional rather than an organic basis. Evidence has been furnished by Major that certain cleavage products of protein related to the guanidine bodies seem to be the ones concerned. For a time it was thought that other endogenous substances play a rôle, such as uric acid and urea, but the chemical examination of the blood of many of these cases fails to support this theory. Our own observations concerning the elimination of phenosulphonephthalein in comparison to the nitrogen content in the blood, would seem to indicate that in these cases the kidney is impermeable to some

substance not related to urea or uric acid. This has not been the experience of other investigators. Fishberg reports high uric acid figures in hypertension although an equally large control series observed by the author where the condition was associated with hypotension showed equally high findings. Recent studies on the relationship of calcium and potassium to hypertension by Kylin has demonstrated an increased content of potassium and a diminished content of calcium in the blood in essential hypertension, *i.e.*, an increased potassium-calcium ratio. It has also been demonstrated that in cases of chronic sympatheticotonus, there is an increase in the potassium-calcium ratio together with an increasing amount of adrenalin and sugar in the blood. The effect of adrenalin injected intravenously on calcium as well as the effect of intravenous injections of calcium on the sensitiveness of the nervous system to adrenalin, represents a new chapter in the study of this disease, and points the way, as will be discussed later under treatment, to a logical method of combatting hypertension. Westfall has shown that cases of hypertension have an increased amount of cholesterol circulating in the blood-stream. Attempts at experimental reproduction of hypertension in animals, by means of the injection of blood-serum taken from cases of hypertension, have revealed some very interesting facts. It has been shown that the injection of this serum even in small amounts causes either immediately, or after a variable interval, a rise in blood-pressure of almost twenty-eight millimeters of mercury. It was further shown that this serum was toxic to animals in amounts of 0.53 cubic centimeter per kilogram of animal, whereas normal serum is toxic only in quantities of eight to twelve cubic centimeters per kilogram. The nature of this toxin has not yet been determined, but it did not appear to be related to the guanidine bodies of Major in view of the fact that the guanidine bodies have a tendency to disappear rapidly from the circulating blood. Recently Major has shown an increased content of guanidine bodies in the blood of cases of essential hypertension.

Other exogenous intoxications which are associated with increased blood-pressure which do not properly belong in the category of essential hypertension are those associated with lead poisoning, with certain metabolic disturbances as gout, diabetes, eclampsia, and infectious diseases such as syphilis. The relationship of syphilis to

Hypertension has been seriously questioned by Walker and O'Hare, who found systolic and diastolic pressures more frequent in control cases than in the series of essential hypertension observed by them. They were inclined to emphasize rather than causal relationship between measles, typhoid fever, and some or chronic rheumatism and hypertension. Endocrine disturbances as a cause of hypertension has been emphasized by various authors. American workers were the first to call attention to the presence of an increased basal metabolism in a certain percentage of cases of hypertension. At the Mayo Clinic, Eccles and Saniford found 10 per cent. of a large series of cases of essential hypertension with a basal metabolic rate of plus sixteen and over. Mannaberg, in Vienna, found an increased basal metabolism of plus thirteen to plus sixty-five in twenty cases with essential hypertension. Hanel found it increased in eight out of thirty cases of hypertension. Boas and Shapiro have reported five cases with a definite increase in the basal metabolism rate and call attention to an important differential point. In hyperthyroids the systolic pressure is high whereas the diastolic is normal or only slightly elevated. They consider this group as a special group belonging in the category of suprarenal and thyroid disturbances in view of the fact that there were no cardiac complications to account for the increased metabolism.

The relationship of emotional disturbances to hypertension has long been recognized by various authors. The effect of autonomic imbalance and hyperthyroid conditions has already been alluded to. The frequent association of essential hypertension with ovarian or testicular dysfunction must be very evident to the clinician from the common occurrence of this condition during the period of the male as well as the female climacterium. Clinically the evidence of gonadal dysfunction and pituitary hyperfunction are manifest in the physical changes occurring in man as well as woman at this period of life. The beginning growth of breasts in women, the beginning growth of the long bones, the deposit of fat in the abdominal wall, lull in sexual activity concomitant with the persistent hypertension—all suggest that the neutralizing effect of the gonads, the suprarenary, thyroid, and adrenals is diminished or absent. Defective constitutional make-up to hypertension is a very important factor which accounts for its hereditary and family origin. The so-called

those subject to marked psychic or emotional disturbances often show a hereditary predisposition to other forms of vasoneuroses which often lead to hypertension, and they are often associated with other hereditary forms of allergy.

The symptomatology of the essential form of hypertension is varied. In the benign types, the increased blood-pressure may be the only symptom and may be disclosed only as a result of an examination for life insurance or a periodic health examination.

Malignant hypertension in some instances develops from the benign type, whereas in other cases it may be malignant from the very outset. The type which develops into the malignant form represents a small minority of the total number of cases which one encounters. The prognosis in this type of the disease is very poor and the treatment of this condition has, up to the present time, been very unsatisfactory.

The clinical symptoms, as summarized by Rowntree and Adson, of the malignant type are: (1) Persistent elevation of the systolic blood-pressure with a very high diastolic pressure; (2) cerebral symptoms consisting of dull headache, irritability, insomnia, mental deterioration, somatic changes in personality and at times apoplectic or epileptiform seizures; (3) loss of visual acuity secondary to neuroretinitis and consecutive to hypertensive changes in the retinal vessels, constriction, spasm, hemorrhages, *etc.*; (4) gastro-intestinal disturbances, especially epigastric discomfort and nausea and vomiting; (5) cardiac changes, enlargement, and at times dilatation with its accompanying train of symptoms; (6) involvement of kidney, nocturia, albuminuria, cylinduria, and sometimes eventually renal insufficiency and (7) asthma, which may be the outstanding feature. So striking are the cerebral features that brain tumor is sometimes diagnosed. The extent to which cerebral, cardiac, and renal manifestations participate probably depends on the relative involvement of the vessels to these organs. Death results in order of frequency from cerebral vascular accidents 50 to 60 per cent., from cardiac failure 20 to 30 per cent. and from renal insufficiency 5 to 10 per cent., the other deaths occurring from intercurrent diseases. The course of the disease is rarely longer than two years, during which time the patient as a rule suffers intensely from headaches, visual

disturbances, or manifestation of cardiorenal vascular disease and is largely incapacitated for work.

It can be seen from the above limited discussion of the various factors involved in this disease, how impossible it is to generalize regarding its treatment. This is particularly true in the secondary type of hypertension, either cerebral, arteriosclerotic, nephritic, or where cardiovascular complications occur.

In this disease just as in similar affections of a chronic nature, the treatment must be governed entirely by the status of the individual. The indications for treatment must be laid out along the lines noted above. General treatment is of value particularly in the mild and moderately severe types. The treatment of the malignant type of hypertension still remains purely palliative. The course of the disease rarely lasts longer than two years, and all that can be accomplished is to make the patient comfortable until the inevitable cerebral, cardiac or nephritic "blow-out" takes place.

In the first two types, the psychic treatment is paramount. Rest in bed if necessary or occupational rest cannot be over-emphasized. This should be instituted until the patient can cope with his surroundings, and secure the necessary adjustment whereby he is exposed as little as possible to enervating and disturbing influences. Sometimes a change of occupation is mandatory and should be insisted upon. Mental rest can also be aided through the use of nerve sedatives, bromides, chloral, neurosine, valerian and even codeine. Hydrotherapy and physiotherapy are of no little value in this connection. Auto-condensation and hot baths may be advisable for subacute and chronic cases. Change to a warm climate occasionally makes life fairly comfortable for hypertensive cases. Attention to hygienic measures must be impressed on the patient. Eliminative therapy will be discussed later.

Dietetic therapy of hypertension is still the subject of considerable discussion. The experimental evidence contributed by Neuberg and Marsh, who produced changes in blood-vessels in rabbits by high protein feeding, and that of Nuzum, Osborne, and Sansum, who produced hypertension experimentally in rabbits by feeding high protein diets containing 20 per cent. liver, is contradicted by the evidence furnished by Weinberg of Paris, who found atherosclerotic changes only in herbivorous animals, and none in carnivorous ani-

mals. In this connection it might be well to recall the observation of Miles in 1907, on the normal occurrence of atherosclerosis in rabbits. Clinical experience would seem to indicate that meat diets do not play the important rôle which was formally ascribed to them. We have maintained a number of patients on protein diets without having observed any demonstrable increase in the blood-pressure. The recent studies of Dubois who observed two men on exclusive meat diets for over a year showed similar findings. The relationship of carbohydrate to hypertension was stressed recently on the basis of the high sugar findings in the blood in these patients. It is important, however, to remember that any toxic substances which produce a discharge of adrenalin into the blood, or any emotional influences which may stimulate the excretion of adrenalin into the blood may be followed by an increase in the blood-sugar concentration, and that this may have no relation to the carbohydrate intake. The increased amount of cholesterol similarly does not bear any relation to the amount of fat which may be ingested. It is probably more likely an evidence of adrenal hyperfunction. What is of considerable moment is the fact that obesity is often associated with hypertension, and that considerable improvement is often observed in the hypertension with a reduction in weight. The diet in hypertension should be one which does not take into account the withdrawal of any one of the basic food constituents, but rather should be one determined by the basal metabolic rate, calorie requirement, and the essential protein, carbohydrate, mineral, and fat requisite for bodily maintenance and energy output. The question of the mineral metabolism of the body is fairly important. Allen's contention of the relationship of salt retention to hypertension has not been borne out in practice (experiments with sodium chlorid in the treatment of thromboangiitis obliterans). Silbert's and Samuels' cases, treated with large amounts of 5 per cent. saline solution intravenously, for thromboangiitis obliterans or arteriosclerotic gangrene, failed to show any increase in blood-pressure even after five years of treatment.

The relationship of calcium to potassium has been previously pointed out. The value of calcium as a hypotensive agent was touched on. Its value as a diuretic in the form of the chlorid or the lactate has been confirmed by the experimental investigations of Addis and his co-workers, and Keith and his group of the Mayo

Clinic. In fact, they suggest that the milk cure is not entirely a dietetic cure, but rather a drug cure because milk represents a 1 per cent. solution of calcium lactate. It has been shown that the administration of calcium chlorid or calcium lactate increases diuresis because of the increased elimination of the acid ion, particularly the chlorin ion, and also that it increases the excretion of sodium which combines with the excess of acid ions. In this way excessive sodium chlorid is removed from the body with the retained water. Several Germans have suggested gastric drainage with histamine subcutaneously to accomplish the same end. Major's experimental work with calcium and methyl guanidine is of particular interest in this regard. He has shown that the blood-pressure raising effect of guanidine can be completely neutralized by calcium as well as liver extract. The active principle of the parathyroid gland prepared by Collip which increases the calcium content of the blood, similarly neutralized guanidine so that the subsequent injection of methyl guanidine sulfate fails to raise the blood-pressure.

The use of vasodilator drugs is often disappointing. Results are often transitory although their use is imperative at certain times. Of this group the most efficacious seems to be nitroglycerin hypodermatically or under the tongue. Oral administration is somewhat less effective. Sodium nitrite by mouth, or intravenously as the French prefer to give it, occasionally brings the pressure down. It does not always follow that a case is not one of essential hypertension because it does not respond to sodium nitrite. Amyl nitrite is variously recommended. I have rarely found it of value. The administration of iodids is of some value, but it should be given by mouth. The use of intravenous solutions of sodium iodid is contra-indicated not only on the basis of Hanzlik's findings, but also because of the severe or fatal reactions that follow intravenous therapy in this disease. In fact, intravenous therapy should rarely or almost never be used where an essential or even secondary hypertension is present.

The use of sodium or potassium sulphocyanate has received a great deal of attention during the past five years. Those who use it consider this drug the most efficacious one, even superior to iodine, for the reduction of hypertension. It is given in doses of from one to five grains three times a day. The Germans administer it under the name of Rhodan, and base its use on the fact that it represents an

anion group which has a definite effect on surface tension of blood and, according to them, acts even more strongly than iodine in this regard. Ayman thinks it is a sedative for the vasomotor nerves. They advise its administration in doses of one and a half grains three times daily for the first week, twice daily the second week, once daily the third week, with discontinuance of the drug for the fourth week. Reports concerning its use are for the most part favorable when large doses are used. It is of little value where renal or other organic changes are well advanced. Benzyl benzoate has failed to prove the claims made for it. Digitalis has been used where cardiac weakness was present with high diastolic pressure above 110.

Eliminative treatment with the use of high colonic irrigations has failed to appreciably modify the high pressure. In our experience it usually increases it in the first few hours following the irrigation. The pressure may come down somewhat in the subsequent days, but it rarely remains down for a long enough period to ascribe any therapeutic value to this procedure. Catharsis or purgation may indirectly modify the pressure by diminishing the absorption of toxic products that may affect the heart or kidneys. Venesection, which properly may be classified as depletion therapy, is indicated at critical periods, and it is advisable at such a time to remove from 500 to 750 cubic centimeters of blood. Lumbar puncture is also of value, particularly where the cerebral symptoms, such as headache and throbbing in the temporal region, become unbearable and the blood-pressure goes to 250 or more. Treatment with non-specific protein, either in the form of milk or with vaccines prepared from foci of infection, occasionally shows surprising reductions in blood-pressure. We have encountered several such cases, particularly where it was associated with some degree of arteriosclerosis who have responded for a time to this method of treatment. The use of liver extracts or extracts from the watermelon seed represent a new departure in the therapy of hypertension. Here the protein factors can be disregarded because most of these extracts are supposed to be alcohol-ether-soluble extracts which contain no protein whatever. Liver extracts prepared by MacDonald in Canada and Major here have proven disappointing in clinical practice. It has been shown that whatever blood-pressure reducing effect followed its use was due to the choline present. Acetylcholine, which is an acetylated prepara-

tion of choline and is 100 times less toxic than choline, has been used for the past few years with varying results. In our experience it does lower the blood-pressure transitorily. According to other workers, it has no effect whatever.

The use of Laura's anti-pituitary serum has given excellent results in his own hands. In others it does temporarily reduce blood-pressure, but fails to maintain this reduction in the essential group for a very long period. A striking fact in the use of most of these substances—liver extract, Laura's serum, potassium sulphocyanate, *etc.*—is the marked subjective improvement which follows. Recently Ayman has shown that even dilute hydrochloric acid will relieve symptoms in 80 per cent. of cases treated, and attributes this relief to the psychic effect exercised by new forms of therapy, and considers that essential hypertension is a form of sympathetic neurosis.

Organotherapy with endocrine substances gives variable results. Thyroid extract in minimum quantities seems to be of some value in cases associated with arteriosclerosis. Ovarian extract in essential hypertension and menopause has not given us any satisfactory results. Insulin in some cases reduce pressure, whereas in others it has no effect. Radiation of the suprarenals or of the skin of the abdomen, or intravenous administration of radium emanation or radium chlorid as a therapeutic procedure has still to be proven.

Barker and Cole have repeatedly emphasized that no universal method for the prevention of the hypertensive diseases can be successfully applied, nor is any single remedy a panacea after the disease develops. It is evident from the above that the old French saying "*Il faut soigner le malade et pas la maladie,*" is particularly true in the treatment of hypertension.

ABNORMAL BLOOD PIGMENTS OF CLINICAL IMPORTANCE

A Clinical Lecture

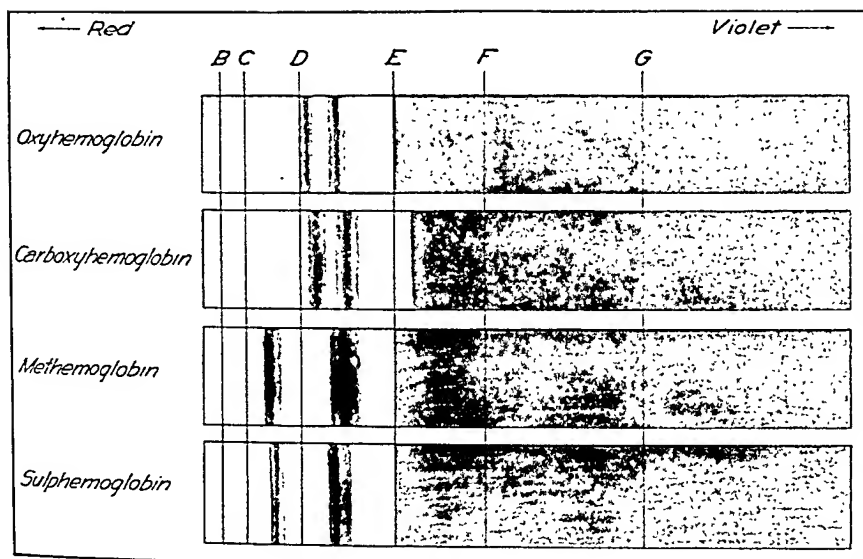
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ALTERATIONS in the color of the blood itself cause several types of abnormal skin and mucous-membrane coloration. One of these is very familiar in the cyanosis of pulmonary, cardiac and circulatory diseases, and as we know is primarily due to an abnormally high proportion of reduced hemoglobin in the superficial skin vessels. When proper oxygenation of the blood does not take place in the lungs, or if, through some anatomic defect, the venous blood is in part shunted directly over to the arterial system without passing through the lungs to be aerated in the normal way, a large amount of unoxygenated hemoglobin will be present in the blood as it is sent to the tissues and its bluish color will produce cyanosis. Similarly, if there is delay in the passage of the blood through the superficial vessels, due to abnormal slowing of the circulation, as in heart disease, the blood will lose a greater amount of oxygen than usual and cyanosis will again result. These mechanisms which produce cyanosis are very familiar to all of you because this is one of the most common of clinical phenomena and has excited attention and interest from the earliest times.

There is still another type of altered skin and mucous-membrane coloration not due to heart or lung disease, but in which an abnormally large amount of reduced hemoglobin may be circulating in the peripheral blood-vessels simply due to the fact that the amount of the total hemoglobin, both oxidized and reduced, in circulation is abnormally great. This is the case in the disease of erythremia or polycythemia vera in which the coloration is due to the tremendous increase in the concentration of hemoglobin and red blood-cells which cram all the available space in the circulatory system and distend the peripheral vessels to more than their ordinary capacity.

FIG. 1.



The Absorption Spectra of Sulphemoglobin and Related Hemoglobin Derivatives

Besides these alterations in skin and mucous-membrane coloration due to qualitative and quantitative changes in the oxygenation of *normal* hemoglobin in circulation, there is still another group of interesting clinical conditions in which very marked color changes occur and which are due to the action of various substances which alter the hemoglobin itself.

The first of these is the condition of carboxyhemoglobinemia, which is due to the formation of the pinkish or cherry-red-colored carboxyhemoglobin, which is produced when carbon monoxide acts on normal hemoglobin. So great is the affinity of carbon monoxide for ordinary hemoglobin—over 200 times that of oxygen—that a comparatively small percentage of this colorless and odorless gas in the inspired air will form a sufficient amount of carboxyhemoglobin in the circulating blood to produce serious symptoms of intoxication by shutting off the proper supply of oxygen, and to cause this curious bright red or cherry-red appearance of the skin and mucous membranes. At first glance the vivid color of these patients may be confused with that of the normal flush due to excitement or exercise, or with the bright red hectic flush of fever. The color is much more striking, however, of a brighter red, combined with pink, and with very little of the bluish element. If a sufficient amount of hemoglobin remains unaltered (about 35 per cent.), and the victim is made to breathe fresh air or oxygen, the abnormal pigment is readily reconverted into normal hemoglobin. (Fig. 1.)

There are two other clinical conditions in which striking alteration of skin and mucous-membrane coloration occurs, due to alteration of the blood hemoglobin itself, and these have been confused frequently in the past with cyanosis, and the condition has often been erroneously ascribed to a heart or lung disease which did not exist. I should like to present an example of one of them that we have had in for treatment for some time in the Osler Clinic.

The patient is a white woman of thirty-five, who has previously been well all her life, with the exception of extreme chronic constipation ever since childhood. For the past five years she has worked for three months each year in a cotton mill, and during this time her hands and arms have been covered with dye-stuffs. During the periods when she was so engaged she had symptoms of headache, and frequent gastric upsets, and at the same time she noticed that

her skin, especially about the face and neck, as well as her lips and tongue, became distinctly bluish in color. Her brother, also a worker with the same dye-stuffs, has had identical symptoms. During the period each year when she was not working in the mill these symptoms gradually disappeared.

When she first appeared here for examination, there was extreme cyanosis of the mucous membranes, without any acute respiratory distress, and without any duskiness of the skin, which, on the contrary, was very pale. She was somewhat confused mentally, very uncoöperative, whining and rather lethargic. She complained of extreme headache, with nausea and vomiting. The retinal veins were of a very striking bluish color. Spectroscopic examination with light transmitted through the ear lobe showed a dark absorption band in the orange part of the spectrum. This was found by measurement to be sulphhemoglobin without any mixture of methemoglobin. A sample of the dye with which she had worked in the cotton mill had a marked odor of hydrogen sulphide which was accentuated on addition of acid. The headache powders which she had been taking for the past month before admission contained each, four grains acetanilid. The urine contained no evidence of blood pigments on spectroscopic examination. With the use of cathartics and colon irrigations, and, of course, cessation of further contact with the dye in the hospital, she has improved quite rapidly. She is now quite normal mentally, her headaches are less severe, and there is no longer any gastric distress. At the present time, after about three weeks of such treatment, the color of skin, mucous membranes and retinal veins appears quite normal. Sulphhemoglobin is still present in the blood, as seen on spectroscopic examination, and, as we shall see presently, is apt to persist for some time.

This appears, then, to be a case of sulphhemoglobinemia, in a person suffering from chronic constipation, which was caused by exposure of the skin surfaces of the upper extremities to some sulphide containing dye. In all probability the prolonged use of acetanilid was also a very important factor in its production.

The common clinical recognition of a curious cyanosis due to the presence of the abnormal blood pigment, methemoglobin, was made first in cases of poisoning with so-called "coal tar" preparations in the aniline dye industry. Aniline and a number of closely

related compounds, such as nitrobenzol and amidophenol, have been implicated in other industries as well in which these compounds are used. Among those are the shoe and leather trades, and in confectionery and perfumery manufacture, particularly on the continent. Many of these compounds have reducing properties, but it has been found that oxidizing agents such as potassium chlorate and permanganate may have the same effect. A fatal outcome in the case of the chlorate when used as a gargle, but taken internally by mistake, has been recorded a number of times. Idiosyncrasy to the drug or faulty kidney elimination may make the condition worse. Among other substances used medicinally which may cause methemoglobinemia are nitroglycerin, the nitrites, and the commonly used analgesics, acetanilid, antifebrin, and phenacetin. The latter drug is converted into paramidophenol, a reducing substance, which causes methemoglobinemia. Characteristic of methemoglobinemia is the fact that unless an overwhelming dose producing a fatal termination is taken, and if the source of the poisoning is removed, the abnormal color or "cyanosis" clears up very quickly, in twenty-four or forty-eight hours.

Besides the methemoglobinemia due to these poisons, which came to be well recognized, scattered cases began to be reported about thirty years ago in which no exogenous agent at all could be implicated as being the causative factor. Stokvis and Talma reported several such cases, and as they were usually associated with gastro-enterologic disorders it was believed that the agent which was responsible must in some way be associated with the intestinal tract. This condition was therefore styled "enterogenous cyanosis."

A little later (1905) Hijmans van den Bergh in studying two other similar patients in whom no exogenous cause for the cyanosis could be found made the surprising discovery that in one of them the abnormal blood pigment was not methemoglobin but sulphemoglobin. This pigment had been known in the laboratory since Hoppe Seyler produced it in 1867 by adding hydrogen sulphide to blood. It had not been recognized clinically before, although, as we shall see, it is very similar in many ways to methemoglobin and often may very well have been confused. The relationship of a disorder of the intestinal tract to the condition was especially clear in this first case of van den Bergh's. It was a child with congenital

atresia of the anus and a urinary fistula and infection. When the condition was relieved by surgical interference the sulphhemoglobinemia also cleared up. Since then reports of a considerable number of cases of enterogenous methemoglobinemia and sulphhemoglobinemia have appeared, but it has never been found possible to produce serious sulphhemoglobinemia by drugs, as in the case of methemoglobinemia. Snapper found it could be done if sulphur was given internally together with phenacetin and this has lent support to the idea that the hemoglobin has to be sensitized in some way before the sulphur can act on it.

During the last three years we have encountered a considerable number of patients in this clinic who have exhibited a constant group of phenomena: cyanosis, headache, chronic constipation, and the record of prolonged use of bromo seltzer, a proprietary remedy which is said to contain acetanilid, potassium bromid and caffeine. On examination all of these patients were found to have sulphhemoglobinemia. Last year we reported a group of ten such patients and subsequently we have collected four more. During this same period it so happens that no patients with methemoglobinemia have appeared in the clinic. This has led us to believe that the condition of sulphhemoglobinemia is, in this locality at least, quite as important a clinical condition as is methemoglobinemia, and that a considerable number of cases which have in the past been diagnosed as the latter condition may in reality have been examples of the former. The error is not difficult to make. An inspection of the chart will show you how similar is the spectroscopic appearance of blood samples containing sulphhemoglobin and methemoglobin and how readily they may be confused if examined only casually. There are several other tests which may be employed. Especially useful is the addition of a few drops of dilute solution of ammonium sulphide to the blood sample. If it contains methemoglobin the characteristic band will vanish but it will persist if it is due to sulphhemoglobin. Still other tests may be found described in a recent article by Doctor Waterfield and myself. (*Jour. Amer. Med. Assn.*, vol. 95, p. 647, 1930).

The types of cyanosis produced by sulphhemoglobin and by methemoglobin are somewhat different. In cases of sulphhemoglobinemia it is usually most marked in the mucous membranes, tongue, and lips. The cyanosis is of a mauve or purplish blue, and the skin

itself may be rather pale with a cream tint, without definite skin cyanosis in mild cases. In methemoglobinemia the color is often a deeper blue with brownish or chocolate shades. This difference is more easily made out if one compares blood containing methemoglobin with that containing sulphhemoglobin. In the one case the brownish or chocolate tint is in striking contrast with the violet tint of the sulphhemoglobin.

For the production of sulphhemoglobinemia it appears essential to have hydrogen sulphide act on the hemoglobin. This may occur either by absorption of a sulphide containing substance through the skin, as in the case we have just seen, or through the production and absorption of hydrogen sulphide from the intestines. This may be due to excessive putrefaction and increased by chronic obstipation. It seems also to be clear from Snapper's observations, confirmed by our own, that the ingestion of phenacetin or acetanilid in some way sensitizes the blood so that small quantities of hydrogen sulphide will then produce sulphhemoglobin. In our cases the syndrome of chronic headache, obstipation, prolonged use of acetanilid (bromo-seltzer), and the cyanosis which is due to sulphhemoglobinemia, has been common. It would seem as though a sort of vicious cycle is set up here which tends to perpetuate itself.

The differential diagnosis between methemoglobinemia and sulphhemoglobinemia is of rather more than academic interest, because of the usual difference in the severity of the two conditions, and of the prognosis. Methemoglobin appears to be an oxidation product of hemoglobin, and unless the intoxication is very severe may be converted back *in vivo* into ordinary hemoglobin without necessarily destroying either the erythrocyte or the hemoglobin molecule. This accounts for the rapid disappearance of methemoglobin in the blood when exposure to the toxic substance which produces it is stopped. Sulphhemoglobin, on the other hand, appears to be a relatively stable substance which is removed only by destruction of the hemoglobin molecule. It may circulate in the blood for a long time before this destruction or elimination takes place, and consequently the cyanosis and the clinical evidence and symptoms of the condition may persist often for very long periods or even years.

We believe, therefore, that many cases in which prolonged use of phenacetin or acetanilid is associated with chronic constipation, headache, and cyanosis are really due to sulphhemoglobinemia and

not methemoglobinemia, and that a careful examination of the blood is warranted in each case on this account. It will be noted frequently in cases of sulphhemoglobinemia that the total concentration of hemoglobin is increased due to the prolonged lowering of the oxygen capacity of the blood. When methemoglobin is present, unless the intoxication continues over a long period, this stimulus does not increase the amount of hemoglobin.

Professor Hijmans van den Bergh (*Klin. Woch.*, p. 1930, 1922) has proposed that the term *parhemoglobinemia* be applied to all conditions in which a change of the hemoglobin into methemoglobin or sulphhemoglobin has taken place, and he divides the various types of parhemoglobinemia into four groups:—first, *intraglobular methemoglobinemia without hemolysis*, a condition which has been met with in severe enteritis with diarrhea. In some of these cases nitrites have been detected in the blood. A second group is that of *intraglobular sulphhemoglobinemia without hemolysis*. In many of these cases, marked disturbance of the proper bowel movements has been observed. A third group is that of *hemolytic methemoglobinemia*, which has been reported in anaërobic sepsis and also in cases of the eclampsia of pregnancy. A fourth group are the cases of *hemolytic sulphhemoglobinemia* which occur in some types of anaërobic sepsis. The two latter conditions are very rare and we have never encountered them here.

Treatment of parhemoglobinemia should be directed to the removal of any offending medicament, and to the efficient relief of constipation. This is essential in cases of sulphhemoglobinemia to prevent the diffusion of hydrogen sulphide from the bowel contents into the blood-stream. For this purpose daily rectal irrigations have often been found effective. Some cases have required surgical interference, and irrigation through artificial openings in the gut has afforded at least temporary relief. The prevention or reduction of hydrogen sulphide formation caused by protein putrefaction in the large bowel may be attempted. The use of intestinal antiseptics for this purpose in our hands, however, has proved ineffective. Hijmans van den Bergh's case in which the cyanosis cleared up when milk was substituted for a meat diet and promptly reappeared over and over again with meat, is very suggestive and points to the possibility of relief of some cases by means of diet.

THE RELAPSING TYPE OF AGRANULOCYTOSIS

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WHILE there is no question that agranulocytic blood-pictures associated with lesions about the oral cavity were described before 1922,¹ the cases described were isolated instances and due credit must be given to Werner Schultz for first presenting a group of cases and calling attention to the condition as a definite syndrome. Subsequent observations have led to a great deal of discussion as to the nature of the process and have made it almost certain that the local lesions are the result of a preceding hematopoietic dyscrasia rather than the cause of a peculiar reaction on the part of the blood-forming organs. It has also become clear that the original picture painted by Schultz is subject to certain modifications. The condition is not confined to middle-aged females—the damage may involve all the elements of the blood, including not only leukocytes but also erythrocytes and platelets, and the course is not necessarily acute.

It is the purpose of this brief communication to record a case in which the disease was characterized by a relatively mild course with temporary recovery and a subsequent fatal relapse. Since this patient was observed in 1929, O. Franke² has described a similar case and has added two others from the literature. It seems worthwhile for the present to record such cases as they probably represent a distinct type of the disease.

A. O., a physician, aged fifty, was seen February 23, 1929, with Dr. Edward J. Whalen, of Hartford, to whom I am indebted for many of the details here recorded.

The patient complained of a swelling on the tongue and an ulceration on the gum.

The family history was without bearing and the only significant points in the past history were that in the early winter of 1928 the patient had Vincent's angina and that in the five months preceding the present illness he had two attacks of tonsillitis. November 2, 1928, during one of these attacks, he had a leukocyte count of 7,200, of which 72 per cent. were polymorphonuclears, 22 per cent. lymphocytes and 6 per cent. monocytes.

The final illness began February 13, 1930, with a slight swelling on the anterior surface of the tongue; this was tender but not spontaneously painful.

About the same time slight ulceration of the gums occurred. There was no fever nor chill at the onset but for two days the swelling increased and the patient felt prostrated. February 17, a severe toothache in the left upper canine tooth developed. The tooth was extracted and this was followed by loss of appetite, pain in the tongue and gums and marked weakness. The patient became irritable, depressed and somewhat apprehensive.

Examination February 23 showed a stockily built and well-nourished man. There was yellowish pallor but no jaundice. There were several old corneal scars, the result of preceding corneal ulceration. On the anterior surface of the tongue to the left of the median line there was an oval elevation measuring 2 by 1.5 centimeters, the center of which was occupied by a yellowish slough 4 or 5 millimeters in diameter. Over an area of gum on the lower jaw, where two molars had been removed years previously, was a shallow zone of ulceration with a necrotic base. A similar condition existed in the socket of the recently removed upper canine. The throat was normal. A few of the cervical nodes in the left posterior triangle of the neck were slightly enlarged. The lungs were clear except for a soft friction rub at the right base behind. The pulse was of medium volume, dicrotic, regular and compressible. The heart sounds were clear but of only fair quality. The abdominal examination was negative, the spleen was not enlarged. There was no sternal tenderness. There was a small furuncle just below the hairline on the right side of the neck. The urine contained a heavy trace of albumen, no sugar, and a few hyaline casts and red blood-corpuscles. The blood chemistry showed rather high blood sugar, 167 milligrams per cent. The smears from the mouth lesions showed rare spirochetes and fusiform bacilli.

The blood-picture was as follows:

February 20—Reds, 4.3; hemoglobin, 80 per cent.; leukocytes, 2.9; polymorphonuclears, 0; lymphocytes, 79; monocytes, 21.

February 22—leukocytes, 2.7; polymorphonuclears, 0; lymphocytes, 83; monocytes, 17.

February 23—leukocytes, 2.3; polymorphonuclears, 0; lymphocytes, 82; monocytes, 18.

The red cells appeared normal. The platelets on February 23 were 210,000.

March 3, 1929, Doctor Whalen reported that there had been little change. The temperature had ranged between F. 102° and F. 104°. Anorexia persisted and the patient took only fluids. The leukocyte count never went below 2,300 but the red cells fell to 2,900,000. March 4 a sudden improvement occurred. The patient asked to be shaved and took an interest in food. The white cells rose to 4,600, of which 45 per cent. were polymorphonuclears, 45 per cent. lymphocytes, and 8 per cent. monocytes. There was no obvious cause for the sudden improvement. During March 29 and 30 the polymorphonuclears again fell to 1 per cent. and 8 per cent. respectively but April 1 they were 44 per cent. and from then until June 18 the leukocyte count ranged between 8,700 and 12,200 and the polymorphonuclears varied from 44 per cent. to 66 per cent. During this period the patient's general condition improved greatly but he developed a small perirectal abscess.

About the middle of June the patient relapsed. He developed great prostration but no local mouth lesions. He finally died September 3, 1929. Jaundice was present for a week before death and a severe and exhausting hiccough

developed twelve hours before death. From June 18 to August 27 thirteen blood counts were made which showed a minimum red count of 3,800,000 and a leukocyte count ranging from 12,300 to 3,100. Between July 3 and August 15 the percentage of polymorphonuclears varied from 70 to 80 but preceding and following this time, *i.e.*, June 18 to July 3 and August 15 to August 27, polymorphonuclears were never found except on one occasion, when 3 per cent. were present.

A study of the whole series of blood counts in this case, which will be found as an appendix to this article, shows that the blood-picture ordinarily described as characteristic of the acute type is not characteristic of the chronic type. It is to be noted in the first place that especially during the period of remission and the final relapse the total leukocyte count varied very definitely with the polymorphonuclear ratio. When the polymorphonuclear ratio was high the total count was normal or even above normal. When the polymorphonuclear ratio was low the total count was generally low, although occasionally as high as 7,500.

One of the most striking things is the rapidity with which the change from an approximately normal polymorphonuclear ratio to an absence of polymorphonuclears took place. For example, on March 1, 1929, the leukocyte count was 2,800 and no polymorphonuclears were found, while on March 3 the leukocyte count was 4,600 and 45 per cent. polymorphonuclears. On June 27 the leukocyte count was 4,200 and there were no polymorphonuclears. On June 28 the total count had fallen to 3,500 but there were 13 per cent. polymorphonuclears, while six days later there were 12,300 leukocytes, of which 80 per cent. were polymorphonuclears. The rapidity with which these changes took place seems to have some bearing on the nature of the process. It has been assumed by some writers that the process is a more or less permanent change in the blood-forming organs, but these experiences make it more probable that the process is in the nature of a toxemia which varies from day to day, the toxin varying in intensity, not only in different cases but probably in the same case, at different times. It is well known that the susceptibility of the different types of leukocytes to toxins varies, the granulocytes being the most susceptible type. There is one other consideration which suggests that the difficulty in this disease is not lack of granulocyte formation, and that is the effect of transfusion. In a recent case seen with Doctor Hutchison, of Hartford, the exami-

nation of the blood after transfusion showed the same lack of granulocytes that characterized the condition before the transfusion, and this notwithstanding the fact that the patient was definitely benefited in a general way. It would seem, therefore, that in agranulocytosis we are probably dealing with a condition of toxemia in which a selective toxin is present which picks out the blood-cells. This, of course, is no real solution of the mystery. It simply takes us a step farther back and raises the question as to the origin of the toxemia.

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APPENDIX
BLOOD COUNTS*

Date	White Blood-cells	Red Blood-cells	Hemoglobin Per Cent.	Neutrophils Per Cent.	Lymphocytes Per Cent.	Monocytes Per Cent.	Eosinophils Per Cent.	Basophils Per Cent.	Myelocytes Per Cent.	Trans. Per Cent.
February 20, 1929..	3,100	1	81	18
February 21, 1929..	2,900	4,300,000	80	79	21
February 22, 1929..	2,750	83	18
February 23, 1929..	2,300	82	18
February 25, 1929..	3,500	3,500,000	60	88	11	1
February 26, 1929..	2,600	83	17
March 1, 1929....	2,800	2,900,000	60	78	17
March 3, 1929....	4,600	45	47	8
March 5, 1929....	6,800	3,200,000	65	55	37	6
March 6, 1929....	10,500	70	26	3
March 28, 1929....	3,200	3,800,000	75	42	55
March 29, 1929....	3,800	1	83	15	1
March 30, 1929....	5,100	8	70	21	1
April 1, 1929.....	8,700	44	46	10
April 3, 1929.....	9,200	51	39	10
April 6, 1929.....	12,200	60	34	5	1
April 10, 1929.....	11,300	4,000,000	75	66	31	1
April 17, 1929.....	8,000	4,000,000	75	56	41	3
April 26, 1929.....	12,800	57	36	5
May 5, 1929.....	9,000	4,000,000	60	38	2
May 17, 1929.....	9,000	4,000,000	80	60	38	2

* From the records of St. Francis' Hospital, Hartford, through the courtesy of Doctor Whalen.

BLOOD COUNTS—(Continued from preceding page)

Date	White Blood-cells	Red Blood-cells	Hemoglobin Per Cent.	Neutrophils Per Cent.	Lymphocytes Per Cent.	Monocytes Per Cent.	Eosinophils Per Cent.	Basophils Per Cent.	Myelocytes Per Cent.	Trans. Per Cent.
June 18, 1929.....	3,500	3,800,000	70	69	31
June 20, 1929.....	3,300	64	36
June 21, 1929.....	7,500	3	90	7
June 22, 1929.....	4,500	68	32
June 24, 1929.....	3,100	74	26
June 27, 1929.....	4,200	74	26
June 28, 1929.....	3,500	13	79	14	2	1
July 3, 1929.....	12,300	80	13	5	2
July 9, 1929.....	17,000	85	9	5
July 29, 1929.....	11,500	70	26	4
August 15, 1929....	9,200	70	25	5
August 22, 1929....	5,400	69	31
August 27, 1929....	4,100	68	32

RECOVERY BY CRISIS COINCIDENT WITH QUININE THERAPY OF A CASE OF AGRANULOCYTIC ANGINA

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AN INHIBITION of the leukopoietic activity of the blood-forming organs may be brought about by several known physical and chemical agents, outstanding examples of which are X-ray, radium and benzol. Occasionally, it follows salvarsan administration. The resultant blood-picture is also seen in reaction to acute infection. The different organisms reported recovered from throat or blood in such cases are staphylococcus albus and aureus, streptococcus, pneumococcus, *B. pyocyaneus* and *B. coli*.

Very commonly an agranulocytic blood-picture, whether induced by radium, salvarsan, or an infection, is accompanied by ulceration of the throat. In examples of each seen by the author, films made from the ulcerated areas showed the characteristic findings of Vincent's angina. These organisms are found also in the ulcers of the throat and mouth which are common in the aleukemic stage of acute myeloblastic and chronic myeloid leukemia. It would seem from this that the ulcerations are related in some way to the absence of polymorphonuclear cells in the blood and that these Vincent's angina organisms are secondary invaders.

On the other hand, in clinical Vincent's angina the ulcers are present in a febrile condition without blood dyscrasia other than a mild polymorphonuclear leukocytosis which might be expected to accompany any infection. Infectious mononucleosis often shows the ulceration with the typical organisms associated with a mononuclear leukocytosis. In this condition the absolute number of polymorphonuclear cells may be slightly elevated, remain normal, or be a little below normal. The increase in mononuclear cells is of normal cells and irritation forms of diverse morphology. Gorham, Smith and Hunt¹ have succeeded in producing a mononuclear leuko-

cytosis in animals by inoculation of either living or dead cultures of the spirochetes from the throat ulcers of these cases. The isolated strains of several patients showed cross agglutination. These studies indicate that the organisms of Vincent's angina have a direct etiological influence in this condition.

Since the report of six cases by Schultz,² in 1922, it has been customary to separate from the others mentioned above the acutely febrile cases with very severe agranulocytosis. These are called agranulocytic angina. Kastlin³ reviewed forty-three cases reported up to 1927 and Ordway and Gorham⁴ brought the number up to 106 in 1930. These patients have high fever and extreme prostration. Most run a rapidly fatal course of several days to several weeks. The outstanding feature is extensive ulceration in the throat and mouth which may involve tonsils, pharynx, uvula and gums. Ulceration of the vagina, urethral orifice and even the anal region has been reported. In some cases the spleen is palpable but not greatly enlarged and some general glandular enlargement may be present.

The condition was originally presented by Schultz as a definite clinical entity. The different organisms mentioned above as cultured from these cases of agranulocytosis in reaction to acute infection suggest that the agranulocytosis is dependent upon the reaction of the host to different bacterial poisons rather than to the specific effect of one organism. The very suggestive work of Gorham, Smith and Hunt, who showed the ability of the organisms of Vincent's, so commonly seen in agranulocytic angina, to produce a leukocytosis in which only mononuclear cells take part, cannot be overlooked in this connection. Infectious mononucleosis is predominantly a disease of vigorous young adults, and agranulocytic angina of the fifth and sixth decades of life. It is easy to imagine the leukocytosis of uncomplicated Vincent's angina, the mononuclear leukocytosis of infectious mononucleosis, the agranulocytosis of agranulocytic angina, and even the clinical picture of acute myeloblastic leukemia to be a reaction different in degree rather than in kind. The suggestion that all these conditions may be caused by one infecting organism and that it is the spirochete of Vincent's angina demonstrable in practically all of them, cannot be denied.

In favor of this is the case reported by Sprunt and Evans⁵ which showed a normal polymorphonuclear response to an acute infection a few months after recovery from infectious mononucleosis. Against this hypothesis is the fact that several patients who recovered from agranulocytic angina had subsequent attacks. It also must be kept in mind that the organisms of Vincent's angina are found in the ulcers associated with the agranulocytosis induced by chemical agents as radium and salvarsan.

Until this confusion is cleared it is essential that all cases showing special features should be reported. The one here presented is believed to be unusual in the nature of the recovery and circumstances under which it occurred.

Case History.—The patient, a physician fifty-seven years old, very active in country practice, was admitted to the hospital May 22, 1929, on the service of Dr. C. C. Sandels, complaining of a sore throat. For six weeks prior to admission he had had a "grippy cold" but continued to work hard. Four days before admission a severe sore throat with fever and prostration developed.

The family history revealed no hereditary tendencies.

The past history was unimportant except for typhoid fever at age twenty-two, and a period of supra-orbital neuritis at age fifty-four, for which he did not stop work. One year after this and two years prior to the present admission, the patient was in the hospital for drug addiction, taking every day four grains of morphine hypodermically and thirty grains of veronal by mouth. After five and one-half weeks in the hospital he was discharged free of the drug addiction and relieved of the neuritis.

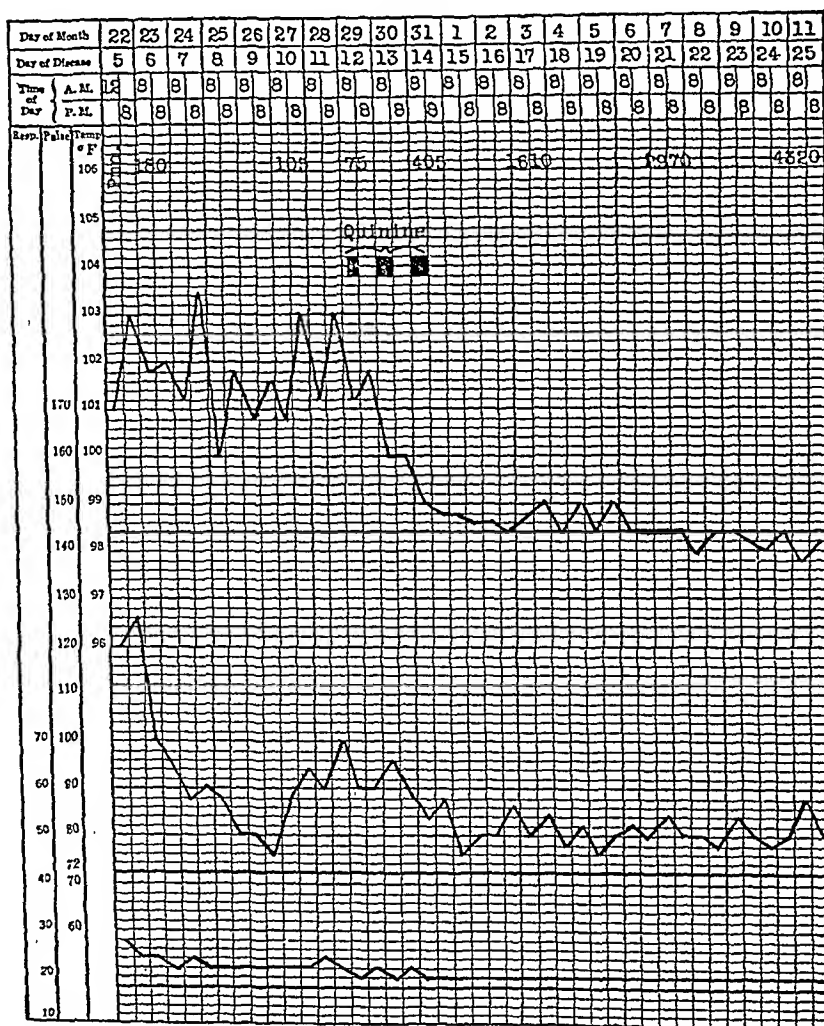
On admission the temperature was 101°, pulse 120, respiration 28. The physical examination revealed a well-preserved and developed man of spare build in extreme prostration. Both tonsils and the uvula were swollen and inflamed. On each tonsil there was a whitish-gray membrane, easily removed with no bleeding. The submaxillary glands were swollen and tender. Over the back, chest and thighs there were a few purpuric spots. The inguinal and epitrochlear glands were enlarged but not tender. The spleen was palpated at the costal margin. The edge was sharp. No other abnormal findings were noted. The blood-pressure was 130/80.

Microscopic films made from the ulcerated areas of the throat on admission and five days later showed the characteristic findings of Vincent's angina. A throat culture during this period showed no organisms of diphtheria but was positive for streptococcus and pneumococcus. The Wassermann test and agglutination test for *B. melitensis* were negative. The admission white blood-cell count was 2,000 with 9 per cent. polymorphonuclear cells, a total of 180, and 89 per cent. lymphocytes, a total of 1,780. The remaining 400 or 2 per cent. were of the large mononuclear-transitional cell group.

During the succeeding six days until May 27 the treatment consisted of the usual measures. For discomfort the patient was given an ice-collar and

five grains of powdered aspirin on his tongue every three hours. Calomel in divided doses and magnesium citrate were used as a laxative. Beginning two days after admission, 8 per cent. arsphenamine in glycerin was applied to the ulcerated areas in the throat several times a day. Seven days after admission

CHART I.



Lilly liver extract 343 was started, three ampules daily. For restlessness six grains of chloralhydrate, twenty grains of sodium bromide and one tablet of allonal were used alternately. There was no improvement in the local lesions or in the general condition. The temperature fluctuated between 100° and 103 2/5°. On the seventh day after admission, May 28, the blood counts were:

red blood-cells, 4,060,000; hemoglobin, 80; white blood-cells, 1,500, with 5 per cent. polymorphonuclear cells, 92 per cent. small lymphocytes, 2 per cent. large lymphocytes, and 1 per cent. large mononuclear-transitional cells. The total number of myeloid cells had decreased rapidly to but seventy-five on this day. (See table.)

On the day following this count, May 29, twenty grains of quinine sulphate were given at noon and again at 6 P.M. The same dose was given three times a day for the next two days, a total of 160 grains of quinine sulphate in three days. By the third day there were 405 polymorphonuclear cells and thirty myelocytes counted. Three days later, June 3, there were 1,610 polymorphonuclear cells and seventy myelocytes. The next day, the fourth after quinine had been stopped, there were 2,662 polymorphonuclear cells and 296 myelocytes. Six days later, prior to discharge as well, all counts were normal: red blood-cells, 4,410,000; hemoglobin, 90; white blood cells, 6,000; with 72 per cent.

TABLE I

Date	Red Blood-cells	Hemoglobin Per Cent.	White Blood- cells	P. Per Cent.	S. L. Per Cent.	L. Per Cent.	M. T. Per Cent.	Myelocytes Per Cent.	Abs. No. Polymor- phonuclears	Abs. No. Lymphocytes
May 23, 1929..	2,000	9	88	1	2	180	1,780
May 27, 1929..	1,500	7	85	7	1	105	1,380
May 28, 1929..	4,060,000	80	1,500	5	92	2	1	75	1,410
May 31, 1929..	4,030,000	80	1,500	27	62	6	3	2	405	1,020
June 3, 1929...	4,150,000	80	3,500	46	40	8	4	2	1,610	1,680
June 6, 1929...	4,930	54	32	6	2	6	2,662	1,873
June 7, 1929...	4,290,000	85	4,950	60	30	6	4	2,970	1,782
June 10, 1929..	4,410,000	90	6,000	72	22	4	2	4,320	1,560

polymorphonuclear cells, total 4,320, 22 per cent. small lymphocytes, total 1,320, 4 per cent. large lymphocytes, and 2 per cent. large mononuclear-transitional cells. (See table.)

The second day of quinine administration the temperature became lower, attaining normal the third day. After this it did not go above 99°. Several days later it became normal and so remained. (See chart.) During this period the throat healed rapidly.

The patient was not seen again and it was difficult to keep in touch with him. The subsequent history may be presented best by quotations from a recent letter from his son. "He had recovered from a second attack of agranulocytic angina around February 15, 1930 (attack), when on March 29, 1930, by lobar pneumonia, death was during the second attack the of my knowledge the treatment given at the West Penn Hospital. After recovery a second attack occurred. It might interest you that I count fell to the best the second attack to that the third attack was

omitted. Doctor M. . 's recovery from the second attack appeared to be very complete and he was apparently in the best of health at the beginning of the third attack."

It is impossible to determine the true significance of this case history. Some patients with agranulocytic angina recover, but not characteristically by crisis as did this patient. The immediate change for the better with the administration of quinine sulphate in relatively large doses seems more than coincidence. The antipyretic action of quinine would explain the depression of the fever only during and for a short while after its administration. It could not explain the rapid improvement of the blood to normal counts in ten days, which proved to be permanent. The healing of the throat lesion coincident with the development of normal temperature and the return of the blood to normal is practically conclusive that the etiologic agent had been removed. The sudden character of the clinical improvement suggests the operation of a specific agent.

If the etiologic agent in agranulocytic angina is an infection or several different infections each capable of inhibiting myelopoiesis, it is possible the quinine had a relatively specific effect for the infecting organism here concerned. More probably it is not generally specific for the organism in question but was given, by fortunate chance, just at the time in its life cycle when it was, or when the reaction of the host toward it had rendered it, susceptible to its effect. In this connection one thinks of the similar action of salicylates, frequently but not constantly seen in acute rheumatic fever. One should also keep in mind the suggested etiologic relationship of infectious mononucleosis, Vincent's angina, agranulocytic angina, the occasional acute febrile patient with no ulceration and agranulocytic blood-picture, and even some cases diagnosed acute myeloblastic leukemia in an aleukemic stage. Until this problem has been solved, the results of quinine in this case suggest that it might be of value in these conditions. The therapeutics in all is unsatisfactory.

Owing to the rarity of these diseases no properly controlled cases have become available for study since the one here reported. This case history is presented for any suggestion for therapy it may contain.

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APPARENTLY BENIGN CHRONIC LYMPH-NODE ENLARGEMENT WITH AT ONE TIME A MONONUCLEOSIS IN THE BLOOD

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A DEFINITELY marked lymph-node enlargement, either local or general, usually suggests at once the probability of one of several serious diseases with unfavorable prognoses, as, for example, tuberculosis, syphilis, Hodgkin's disease, lymphosarcoma, or lymphatic leukemia.

There are, however, cases that run a benign course, and it is well to keep in mind the possibility of a favorable prognosis.

Some years ago several observers described the condition now generally known as acute infectious mononucleosis from which the patients spontaneously recover. Formerly, such cases often gave rise to dread of the development of acute lymphatic leukemia.

It may be that this condition has a chronic counterpart; at any rate, it may not be amiss to record this single case of fairly general lymph-node enlargement that has run an entirely benign course for two and a half years with no obvious symptoms. It has been associated at times with a blood-picture suggesting that of acute infectious mononucleosis with the exception that the total leukocyte count has not been increased.

The patient, a man of thirty-eight, was first seen on November 30, 1928, when he complained of nervousness during the preceding year and a half. The chief symptom was a feeling in the head as though it would explode or as though he had been struck upon the head. There were many other symptoms, as, for example, palpitation, gaseous indigestion, pains from shoulders to finger-tips with certain movements causing sensations like electric shocks, difficulty in sleeping, poor concentration, poor memory, loss of interest and depression.

He was of the pyknic habitus, of normal nutrition, and had always been of a cyclothymic constitution. His syntonie tempera-

ment had contributed largely to his marked success as a salesman.

The diagnosis made at that time was of an anxiety neurosis with depression.

In the past history there was a long story of alcoholic excesses, the immoderate use of tobacco, and marked dissipations in most of the usual fields. He had contracted gonorrhea several times but gave no history of a syphilitic infection.

At the time of the first examination he was physically sound with the exception of functional disturbances like the spastic colon, slight albuminuria and cylindruria. There was no lymph-node enlargement. There were no obvious foci of infection on careful examination of the gums, of the nose and throat, of the urinary tract or of the abdomen. Wassermann reaction of the blood serum was negative. The cerebrospinal fluid was normal.

He was sent into a nursing home on December 5, 1928, for treatment. About ten days or two weeks after his admission to the nursing home, he himself drew attention to enlarged lymph-nodes in the right side of his neck. They were at that time slightly tender. Within a week the axillary nodes were enlarged, and much later the inguinal nodes were involved. There was never any fever. He was in the nursing home from December 5, 1928, to February 12, 1929, and the temperature was taken twice daily.

The nodes in the neck were at first about the size of marbles, later increasing to that of pigeon eggs, and in the axillae were the size of guinea eggs. They were firm, discrete, and after the first week or two, not tender. During the first few weeks the cervical nodes were the largest, then there was decrease in size of these nodes with more marked enlargement of the axillary nodes, especially on the left side. Not until a year later was there marked enlargement of the inguinal nodes and of the epitrochlears.

A node was excised from the right side of the neck for histologic examination. The histologic picture was that of ordinary lymphatic hyperplasia with the architecture of the node preserved, with great increase in the lymphoid cells, many mycotic figures, a few eosinophils and some increase in the endothelial cells, but no fibrosis, no giant cells, no evidence of acute inflammation nor of an infectious granuloma.

The examinations of the blood before the onset of the lymphatic

disease and during the first few months after its onset were quite normal. About one year after the beginning of the lymphatic enlargement, November, 1929, and again in February and in March, 1930, the differential formula of the white blood-cells was definitely changed, although there was no increase in the total number of leucocytes. The mononuclear elements were about 60 per cent. of the total count. The smears examined microscopically showed a variation in the appearance of the lymphocytes with the normal small lymphocytes, the usual larger lymphocytes, and a number of immature forms or pathologic lymphocytes quite similar to those observed in acute infectious mononucleosis.

The clinical course of the nervous disorder has been quite typical of the relatively mild but long-drawn-out affective disturbances. For the past two years he has been able to work but is frequently distressed by exacerbations of the nervous symptoms. Repeated examinations have revealed no foci of infection. Recent Wassermann reactions and precipitation tests of the blood serum have been negative. X-ray examinations of the chest have been negative. Neither the spleen nor the liver has been palpable at any time.

At the latest examination, in April, 1931, the following note was made about the lymph-nodes: "At the angle of the jaw there are one or two small shot-like nodes. In the right posterior cervical triangle there is one small olive-sized node behind the sternocleidomastoid muscle. In the left side there are two small olives behind this muscle, and in the supraclavicular fossa on the left side three or four nodes the size of buckshot. In the right axilla there is one node the size of a Queen olive; in the left axilla two nodes as large as small walnuts. The epitrochlears are palpable. Inguinal nodes on the left side are not enlarged; on the right side there are three or four small olive-sized nodes. No masses were felt below Poupart's ligament."

After two and a half years the lymph-nodes are smaller than they were during the first year of their enlargement. During the past five or six months the blood counts and smears have been entirely normal. During the period when the blood showed mononuclear increase there were no other unusual features. There has been no direct treatment of the lymphatic disease.

I am quite at a loss to explain the source of the lymphotoxin.

I believe that we can rule out lymphosarcoma, leukemia, and tuberculosis. I do not believe that the patient has Hodgkin's disease, and I feel that syphilis is quite unlikely. No definite positive toxic factors are obvious. The excessive alcoholism had ceased before the onset of this trouble. He had taken sedatives such as luminal and bromides for a year and a half before the onset of the lymphatic enlargement, and has taken luminal, an occasional dial tablet and an occasional novatropin tablet since that time. The patient is unusually free of evidence of focal infection.

The condition, so far at least, seems to be entirely benign.

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Clinical Papers on Diseases of Lungs

CHRONIC BASIC NON-TUBERCULOUS DISEASE OF THE LUNGS

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As SCIENCE advances and new methods of investigation are devised, ways of regarding old problems are altered and morbid states regarded previously as entities are recognized to be in reality assemblies of more or less closely related conditions. In the study of the chronic diseases of the lower respiratory tract, additional data derived from the utilization of bacteriology, of roentgenography and of bronchoscopy have helped to segregate and to identify an increasing number of diseases in which productive cough is a cardinal symptom.

Within a short time after the introduction of methods by which an etiologic diagnosis could be made, it was recognized that most acute and chronic infections limited to the lower part of the lungs were due generally to organisms other than the tubercle bacillus. As long ago as 1898, Fowler and Godlee described nine conditions that they designated as "non-tuberculous basic disease," and with the aid of the procedures mentioned already, at least three other pathologic states were added to those they had classified. Of these non-tuberculous infections of the lungs there is one group that is of especial interest because of the frequency with which it occurs, the diagnostic difficulties that it presents and the consequences to which it may lead.

In 1902, Lord described eighteen cases of a chronic infection of the lungs characterized by a relapsing course and due to the influenza bacillus. In 1913, Riesman reported a peculiar lobar form of bronchopneumonia of long duration occurring in children and in young adults, and in 1915, Larrabee wrote of a subacute type of lobular pneumonia with a lobar distribution involving the lower lobe of the lung. These authors focused attention upon the occur-

rence of somewhat similar types of infection that were limited as a rule to the inferior portion of the lungs.

In 1916, Hamman and Wolman suggested the term "chronic non-tuberculous lung infections" to describe another syndrome associated with pathologic changes that affected usually the same portion of the respiratory tract, and a year later, Garvin, Lyall and Morita elaborated on the subject, and they were followed by J. A. Miller, who endeavored to correlate the acute, the subacute and the chronic conditions referred to as evolutions or phases of the same malady.

The subacute type of infection described by Riesman occurs chiefly in children and young adults. The onset is insidious or is characterized by a coryza and a moderate fever of several days' duration, without marked constitutional symptoms. Cough, slight or severe, productive or non-productive, thoracic pain and occasional small hemoptyses are the cardinal symptoms, but they may be so slight and the patient may be so slightly incapacitated by them that the physical signs seem quite out of proportion to them. A physical examination shows diminished pulmonary resonance, modified breath sounds and numerous moist and occasionally consonating râles in the lower lobe of one lung, unassociated, as a rule, with the somatic evidences of an acute respiratory infection. In many cases, cultures of the sputum show the presence of pneumococci or of the influenza bacillus. The illness lasts from several weeks to several months and terminates always in complete recovery symptomatically and anatomically. The pathologic changes can only be inferred, for no patients have died. Certainly, as Riesman stated, there is more than an ordinary bronchitis, for the signs are those of increased density of the lung itself. A pleurisy would not be adequate to explain the clinical findings, and the symptoms as well as the evolution of the disease indicate that there is not the usual type of consolidation that develops in true lobar pneumonia. Probably, as he suggested, there is a bronchopneumonic infiltration that assumes a lobar distribution by the confluence of several or more areas.

An instance of this type of infection was a lad ten years of age (R. H.) whose family history was irrelevant except that an older brother had two years previously had an illness similar to the one to be described. Always robust, never prone to respiratory infections, and never ill before except for an attack of measles and of

pertussis in earlier childhood, the boy refused his breakfast on February 14, 1929. He had a slight coryza and his temperature was 99.8° F., but otherwise the examination was negative. Irregular, slight pyrexia persisted, headache, listlessness and an unproductive cough developed, but daily examinations disclosed no objective abnormalities except injection of the pharyngeal mucosa until February 22, the ninth day of the disease. At that time there were outspoken dulness, distant tubular breathing, numerous râles and bronchophony over the entire lower lobe of the right lung. These evidences of consolidation of the lung were surprising in view of the absence of a constitutional reaction, for by this time the patient appeared to have recovered entirely. Examination of the blood showed a leukocytosis of 25,200, with a relative increase of the polymorphonuclear cells. The temperature returned to normal within two weeks, the dulness and tubular breathing were replaced by normal resonance and a vesicular respiratory murmur in the same length of time, but râles were present for a month, after which no abnormal signs were detectible.

The subacute type with recurrences described by Miller has the same symptomatology as the syndrome reported by Riesman, but it is characterized by the occurrence of relapses at irregular intervals, each associated with a reappearance of the abnormal physical signs at the site of their original location.

The chronic type of basal non-tuberculous pulmonary infections in our experience occurs with much greater frequency than does either the subacute type or the subacute type with recurrences, and although the clinical picture that it presents is a reasonably characteristic one, it may be confused readily with many other syndromes. Individuals of all ages are susceptible to the malady, but young adults seem more prone to develop it. The initial symptoms develop with maximum frequency during the months when acute respiratory infections in general are most prevalent, namely, in the autumn and winter. The incidence of its occurrence rose sharply after the pandemic of influenza in 1918-1919 and remained higher than during the pre-epidemic era for about three years, since when fewer patients with it have been observed. In no instance has it been possible to relate the development of the chronic type to an illness that conformed to the subacute form described by Riesman, but the evo-

lution from the subacute type with recurrences seemed to be established in several patients. The onset of the symptoms may be insidious after a "cold on the chest" or an attack of bronchopneumonia, or with the manifestations of a respiratory infection that developed after measles, pertussis or influenza. There is no evidence available as to the mode of contracting the infection, none to indicate that there is dissemination by contagion for no instance of more than one case in a household has been encountered. At first, cough with or without expectoration may be seasonal or endure throughout the year. Later, these symptoms increase and are complicated by recurrences of slight fever, prostration, myalgia, arthralgia and headache, manifestations that persist for several days and suggest a mild influenza. For some time during these acute exacerbations there may be no signs to indicate that there is any disease of the lungs, but ultimately the clinical findings may suggest either a tuberculous or a non-tuberculous pulmonary infection. In brief, the cardinal symptoms are periodic cough with expectoration that, transitory at first, is recurrent from time to time, and finally becomes chronic; occasional fever, malaise and thoracic pain that may be due to an acute pleurisy. In spite of the persistence of these manifestations for months or even for years, there is only an insignificant impairment of the general health, although there may be anorexia, lessened endurance and the other constitutional disturbances that occur so regularly in phthisis. Hemoptysis occurs in about 50 per cent. of the cases and this symptom with the others enumerated leads oftentimes to an incorrect diagnosis of tuberculosis.

Physical examination shows generally good preservation of nutrition and an absence of cyanosis, of pallor and of dyspnea. In a majority of the cases there is evidence of a chronic infection of the upper respiratory tract—rhinitis, sinusitis, pharyngitis, tonsillitis—or a state of oral sepsis, and it may be that now and again the pulmonary infection starts from such loci. Clubbing of the fingers, although it is not a constant happening, develops early in some cases and with much greater frequency than it does in pulmonary tuberculosis. A thoracic examination reveals abnormal signs, limited, as a rule, to the lower half of the chest—in our experience more often on the left side than on the right. As a rule, inspection and palpation disclose no abnormality and the localized diminution of

resonance that may be detected in the subscapular region, in the lower posterior axilla or at the extreme base of the lung, may be only trivial. In such a circumscribed area of altered resonance the respiratory murmur may be normal in some cases, distant or intense in others, or there may be bronchovesicular or even tubular breath sounds. But the sign found most constantly is râles. It has been well said by Garvin that in the absence of cardiac disease, persistent, unilateral, localized basal râles are almost pathognomonic of this disease. Not infrequently, the adventitious sounds can be heard during only a part of the day, with or after coughing or when the patient changes his position to an inverted one while drainage of the lung is in progress. Thus, it is apparent that the condition is predominantly one of symptoms. The signs may be very scanty and elusive even when the cough is loose and the patient is expectorating quantities of purulent sputum daily. They may be localized in a small area and may escape detection unless the entire basal region of the lungs, including the areas covered by the lower portion of the scapulae, is explored. In every thoracic examination, therefore, that portion of the chest that is uncovered when the arm is abducted and elevated should be investigated. Broadbent's classification of thoracic aneurysms into those of symptoms, those of signs and those of symptoms and signs might be applied with propriety to the several types of these basal lesions that are encountered, for now and again no abnormal signs can be found although characteristic symptoms are present; focal signs may be many in the absence of subjective disturbances, or objective and subjective abnormalities may be related obviously to one another.

The cough may be frequent and harassing or occur in prolonged paroxysms only once or twice a day. Frequently, it is influenced by a change of position such as stooping or lying prone. The sputum is purulent and varies in amount from a dram or so up to several ounces during the day. Although occasionally bloody, it is not foul, contains no elastic tissue and no tubercle bacilli. Cultures of washed sputum or of secretion obtained through the bronchoscope show a varied flora. In some series, bacillus influenza has been grown in pure culture or has been the predominant organism; in others, pneumococcus type 4, streptococci, hemolytic and non-hemolytic, staphylococci and streptococcus mucosus have been found.

The frequency with which anaërobic bacteria, spirochetes, fusiform bacilli and vibrios occur has not yet been established, but the fact that these parasites have been found in cases of bronchiectasis and of pulmonary suppuration suggests that they may be of etiologic importance in these cases also. It may be that even under normal conditions the bacterial flora of the bronchial tree is the same as that of the mouth but that by means of the movements of respiration, the ciliary activity of the epithelial cells, the tussive reflex and the peristaltic-like movements of the bronchioles and bronchi, these resident micro-organisms are swept out of the air passages. They do no harm unless pathologic changes occur locally and prevent adequate drainage of the respiratory tract. In the few cases of chronic basal infections in which cultures of the sputum on special media incubated aërobically and anaërobically have been made, these organisms have not been found regularly and examinations of fresh preparations with the dark-field microscopic have given negative results. Studies of the blood show little or no anemia and only a slight or a moderate leukocytosis with a relative increase in the percentage of polymorphonuclear cells.

The roentgenographic findings show much variation and not infrequently there are marked discrepancies between the changes disclosed by the film and those demonstrated by the physical examination. Patients with numerous physical signs show frequently insignificant or no radiographic alterations, whereas instances are numerous in which the film shows a localized area of what appears to be a dense infiltration, the presence of which the most painstaking examination fails to detect even with a knowledge of their indicated existence. This latter discrepancy may be due to the site of the lesion or to the fact that it is not anatomically an active one; the former is explicable less readily unless it be admitted that certain types of pulmonary inflammation are permeable to the X-ray and cast no shadow. In spite of the fact that other experience in cases of undoubted lobar pneumonia and of pulmonary tuberculosis proved by the coexistence of symptoms and of abnormal physical signs associated with the presence of tubercle bacilli in the sputum indicates that this may be so, this view has not been acceptable to those roentgenographers to whom it has been suggested. More or less characteristic, when they are found, are increased shadows along

the bronchovascular radiations limited to the basal regions of the lungs or localized areas of incomplete consolidation at this site. The radiographic changes are not to be confused with those viewed so constantly when the patient has had an attack of measles or of pertussis, for these, unassociated with symptoms, have been observed unchanged over a period of years and without the development of clinical illness. Following the intratracheal introduction of an opaque substance such as lipiodol, the roentgenographs show a diffuse lace-work of fine shadows representing the branching bronchi but no evident dilatation of them and no bulbous widening of their ends. The precise significance of these shadows cannot be stated, for, so far as can be learned, there have been no studies reported that establish the different roentgenographic densities to be seen after the introduction of lipiodol into the normal bronchial tree. The observations made thus far in this group of cases indicate the present need of establishing the variety of roentgenographic appearances that may be presented by the injected normal bronchial branching in order that relatively slight abnormalities of them can be recognized.

Examination with the bronchoscope shows swelling and turgescence of the bronchial mucosa and more or less mucopurulent secretion loosely adherent to it or free in the lumina of the bronchi. No dilatation of the larger air-tubes is found and the state of the small subdivisions has not been described because of their inaccessibility to direct view. The latter lack of evidence precludes the detection by this method of cylindrical or localized saccular widening of these more peripheral arborizations. In short, the bronchoscopic findings are essentially identical with those seen in chronic bronchitis.

The course is protracted, lasting several months or many years, and the signs persist generally at the original site and show no tendency to become more extensive. This tendency of the pathologic changes to remain limited to the area affected originally is almost without exception. Bronchopneumonia may develop as a recurring complication. It has been especially interesting to note that in at least six of the cases that we have observed for from ten to fifteen years, a definite bronchiectasis has developed and this observation indicates the potential gravity of the condition, the desirability in

every instance promptly to recognize the disease and to eradicate the infection when that can be done.

The history of one of these patients is illustrative:

In November, 1921, A. S., a white girl nine years of age, came to the outpatient department of the Johns Hopkins Hospital because she had a productive cough. Her parents were living and well and were confident that the child had not been exposed intimately to tuberculosis or to other respiratory infections in the home. Her only antecedent illnesses had been measles, varicella and an attack of typhoid fever at the age of five years. Although she had not had many acute respiratory infections, her tonsils had been removed. A few weeks before she came to the clinic, she developed a cough without constitutional symptoms and this was productive of small amounts of odorless purulent sputum that never contained blood. The physical examination disclosed no objective abnormalities except a few transitory dry râles over the upper lobe of the right lung and the roentgenograph of the chest showed a slight infiltration of the lower lobe of that lung. The sputum was purulent but no tubercle bacilli were found although numerous searches for them were made. Symptomatic treatment was prescribed and periodic examinations were made at short intervals. In June, 1922, because of the persistent cough and expectoration, even though there were no constitutional symptoms and in spite of the good development and nutrition of the child, she was sent to the State Sanatorium for Tuberculosis, where she remained for eleven months. Now and again during the next two years there were times when the symptoms were absent, but in the summer and autumn of 1924 re-examinations showed impaired resonance, modified tubular breath sounds, persistent rhonchi and moist râles over the lower lobe of the left lung and roentgenographic evidence of increased density there. A vaccine of streptococci, staphylococci and micrococcus catarrhalis was prepared and administered, but this treatment and general hygienic measures did not influence the cough or the expectoration. In February, 1925, there were signs of active infiltration at the bases of both lungs and these changes, interpreted with regard to the chronicity of the productive cough, the absence of constitutional symptoms, the constant absence of tubercle bacilli from the sputum, led to a tentative diagnosis of early bronchiectasis secondary to a chronic basal infection.

By December, 1927, the cough had become more persistent, the amount of sputum had increased and that month a hemoptysis occurred. A careful review of the physical status showed no new findings. In May, 1928, because of the continuing symptoms and of the recurrent hemoptyses, a bronchoscopic examination was made and dilatation of the major bronchi to the lower lobes of the lungs was found. Drainage of the profuse, purulent secretion in these tubes and the local application of 2 per cent. silver nitrate had no appreciably beneficial effects.

In March, 1931, it was learned that in addition to the former symptoms there had been febrile reactions lasting for several days, the sputum had been streaked with blood on numerous occasions and several more frank hemoptyses had occurred. The physical, roentgenographic and bronchoscopic findings were essentially unaltered. Examination of the bronchial secretion did not show

tubercle bacilli, treponemata, spirilli, fusiform bacilli or vibrios, but only hemolytic streptococci and diphtheroids. Sulpharsphenamin was administered through the bronchoscope but the symptoms were unaltered. In April, 1931, the sputum varied between thirty and ninety cubic centimeters daily, hemoptyses were more frequent and roentgenographs of the chest after the introduction of lipiodol by the passive method showed evidences of sacculatation at the ends of the bronchi to the lower lobe of the right lung. The left bronchus was not filled.

On April 23, 1931, a portion of the left phrenic nerve was excised and promptly following that operation the sputum decreased to ten cubic centimeters daily, hemoptysis has not recurred, but over the compressed lower lobe of the left lung numerous râles are heard still.

Thus far it has not been possible to foretell which of the patients were likely to have this unfavorable outcome, but it is our impression that the subsequent incidence of bronchiectasis will be greatest in those patients whose early lesion is bilateral and very resistant to the measures of treatment later to be outlined, and in those who have chronic infections of the buccal cavity or of the paranasal sinuses. What rôle is played by the flora considered generally to be responsible for pulmonary suppuration cannot be answered because when these individuals were observed first there was no proper appreciation of the importance of these invaders. In a small series investigated recently they have not been found; however, from now on they will be looked for in every instance, particularly in view of the observations of Hedblom, who has demonstrated the presence of these organisms in the bronchial secretion of patients with bronchiectasis and has produced that disease experimentally in animals by infecting them intrabronchially with them. That in many cases bronchiectasis may have its genesis in such chronic non-tuberculous infections of the lungs may be suspected for several reasons. (1) The chronic infection leads to weakening of the bronchial walls, localized atelectasis and fibrosis of the lung removes support from them, and may even cause some traction on them, and the stasis of the bronchial secretion plus the increased intrabronchial pressure with coughing furnish the mechanical factors to dilate the air tubes. (2) Hamman and Wolman found in the one patient that was examined postmortem a small empyema and in the lower lobes of the lungs scattered areas of bronchopneumonia and dilated bronchi filled with purulent secretion. (3) The influenza bacillus was shown during the pandemic

of 1918-1919 to cause not merely bronchitis but a necrosis of the bronchial walls penetrating their entire thickness and leading to fissures or tears extending from the lumen to the alveoli so that retained viscid secretions, gravity and tussive effort led readily within a few days to dilatation and sacculation of such affected bronchi. That perhaps other organisms may act in similar manner may be assumed and what seems surprising is that the unfavorable evolution of the syndrome under consideration is not more frequent. Perhaps the variation of the invading bacterial flora may be a determinant.

The outlook of the uncomplicated cases is excellent so far as life is concerned, but poor when the return to complete restitution of health is considered. Although now and again exceptional instances of spontaneous subsidence of all symptoms may be encountered, it has been our experience that, once established, the process is prone to persist indefinitely and to lead occasionally to the development of manifest bronchiectasis. In spite of the fact that some cases of asthmatic bronchitis develop physical and roentgenographic signs of infiltration of the basal portion of a lung, paroxysmal dyspnea is a relatively uncommon symptom of the usual type of non-tuberculous infection under discussion.

Differential Diagnosis.—The symptoms and signs of these basal infections, although more or less characteristic, are so like those encountered in many other diseases of the bronchi and lungs that a differential diagnosis may be extremely difficult at times.

Tuberculosis of the lower lobes without involvement of the infra-clavicular or apical regions is usually a progressive disease with marked toxic or constitutional symptoms, deterioration of general health, dyspnea and cyanosis. Oftentimes a history can be obtained of intimate, prolonged exposure to tuberculosis, of chronic otitis media, of adenitis or of keratitis in childhood. Tubercle bacilli are usually present, elastic tissue may be demonstrable in the sputum, and a lymphocytosis is more usual than a leukocytosis. Clubbing of the fingers may develop but it does not as a rule unless there is a cavity or fibrosis with a secondary bronchiectasis. The roentgenograph may show the presence of an active or of an old healed focus elsewhere in the lungs or in the mediastinum, and the response to tuberculin may be outspoken. A careful consideration of the his-

tory, of the physical findings and of the results of the study of the sputum and the blood should minimize the unnecessary frequency with which tuberculous and non-tuberculous disease of the lower lobes of the lungs are confused. If the non-tuberculous infection is localized in the upper third of a lung, the clinical course of the disease, the continued absence of tubercle bacilli from the sputum and the roentgenographic findings are the means to differentiate it from phthisis.

Chronic bronchitis is secondary as a rule to some other discoverable pathologic state, occurs more often in middle or in old age and in addition to a seasonal cough is characterized by dyspnea of varying severity and an absence of fever and of constitutional deterioration. When of long duration it may lead to the development or to the aggravation of emphysema or may be followed by severe bronchiectasis. The pathognomonic physical finding is the presence of a diffuse bilateral distribution of rhonchi and of moist râles and at times a prolongation of expiration without any diminution of pulmonary resonance, or any significant alteration of the respiratory murmur other than perhaps the prolongation of expiration. Examination with the Roentgen-ray with or without the intratracheal introduction of lipiodol in uncomplicated cases shows no infiltration of the parenchyma of the lungs and no more than a slight widening of the bronchial ramifications.

Mycotic infections of the lungs, although they are of relatively infrequent occurrence, present now and again a real diagnostic problem. However, the presence of more or less characteristic dermal lesions in blastomycosis, sporothricosis and coccidiosis and of discharging sinuses about the neck and chest in actinomycosis suggests an infection with a fungus and leads to a search for it in the accessible lesions as well as in the sputum.

Hydatid cysts of the lung occur generally in the lower lobe of the right lung. They may be recognized when an individual who has had much to do with dogs develops recurrent hemoptysis and shows evidence of a circumscribed, rounded area of pulmonary disease, has an eosinophilia, a positive complement fixation test with echinococcus antigen or hooklets in his sputum. Chills, fever and urticaria are usual symptoms in some cases.

Tumors of the bronchi and lungs may give rise occasionally to

precisely the same local thoracic signs as basal infections do, but the collateral evidence will suffice usually to differentiate between them. Benign tumors of the lower respiratory tract are rarely met with and when they are present, the roentgenograph and bronchoscope serve best to identify them. Primary malignant neoplasms are prone to lead to gradual or at times to rapid impairment of health and of nutrition, to dyspnea and to the development of anemia. If the new growth occludes a bronchus there will be the signs of atelectasis or if it invades the pulmonary tissue the signs of infiltration will increase. Usually bacteriologic, roentgenographic and bronchoscopic studies will indicate the diagnosis in doubtful cases. Metastatic tumors of the lungs are to be suspected if atypical intrapulmonary signs are found, especially when there is a malignant growth of the adrenal glands, the prostate, stomach, breast, thyroid or testicle. The constitutional reaction of the patient, the anemia and the sharply circumscribed, round or oval, usually multiple uniform shadows of increased density shown in the roentgenograph are diagnostic.

Ordinarily, an abscess of the lung should be readily differentiable from the type of infections under consideration, for the history and the clinical course are suggestive even when the focal signs are few. Localized pulmonary suppuration is most often a sequel of a surgical operation, the aspiration of a foreign body, of pneumonia or of thoracic trauma and primary abscess occurs only seldom. Hence the history may indicate the probable diagnosis when the nature of the local lesion is in doubt. Moreover, when there is an actual abscess of the lung, the onset of the symptoms is abrupt, the constitutional disturbances are marked, septic fever, chills, sweats, anemia, high leukocytosis, loss of weight and clubbing of the digits are progressive. As a rule, thoracic examination shows not only infiltration of the pulmonary tissue but signs of cavity as well and if the local disease is of long duration some evidences of amyloid disease may be apparent.

Now and again, when an encapsulated interlobar empyema has ruptured into the lung and drainage into a bronchus has been established, the signs may be indistinguishable from those of a primary basal infection. Generally, however, the history of the beginning of the illness, the more severe general reaction and the roentgeno-

graphic localization of the pathologic changes suffice to establish the correct nature of the condition. Similarly, difficulty may be encountered when an abscess of the liver has invaded the lung, though in that event a history of antecedent digestive disturbances, of jaundice and of general symptoms together with the high fixed position of the diaphragm or the discovery of *entameba histolytica* in the feces or in the sputum prove the source of the pulmonary disease.

Pneumoconiosis affects both lungs more or less equally, causes dyspnea of varying severity and results in extensive bilateral changes recognizable by the roentgenographic appearance of them. Asbestosis of the lungs, a particular form of pneumoconiosis that has attracted some interest of late, occurs in workers in asbestos, leads to cough, hemoptysis, extreme dyspnea and to emaciation that is out of proportion to the signs of pulmonary disease. The examination of the sputum may show the presence of characteristic golden yellow asbestos "bodies" and the roentgenographs show often obliteration of the costophrenic angle and have a ground-glass or finely mottled appearance, the evidence of a fine fibrosis of the lungs.

Localized primary unilateral basal bronchiectasis that has not led to the formation of a large bronchial sacculum or a bronchiectatic cavity cannot be differentiated from the condition under discussion without roentgenography and then as a rule only when the bronchi have been filled with some opaque substance such as bismuth or lipiodol, for the symptoms and the physical signs of these two conditions may be identical. When so-called contrast plates are made, the presence of definite dilatations of the bronchial ramifications shows that the condition is no longer one of simple basal infection, so-called.

When bronchiectasis develops as a consequence of fibrosis of the lungs due to tuberculosis, collateral evidence of chronic extensive pulmonary disease or the demonstration of tubercle bacilli will indicate generally the underlying cause; when it is secondary to pneumoconiosis, the history of exposure for years to the inhalation of abrasive dusts, the dyspnea, the bilateral extensive distribution of the signs and the uniform mottling and striae seen in the roentgenographs will reveal the nature of the changes; if it is the result of atelectasis due to the occlusion of a major bronchus by a foreign

body, the history of onset, the limited movement of the affected side, the elevation of the homolateral leaf of the diaphragm, the dislocation of the mediastinal structures toward the area of collapse, the roentgenographic and the bronchoscopic findings will furnish the needed evidence to clarify the picture as will hemotologic, general clinical and radiographic studies when the bronchi are obstructed by a mediastinal tumor. Finally, if the bronchial dilatation follows the collapse of the lung as a result of a pleural effusion, the extent of the pleural involvement and the deformity of the chest will suffice to show its origin.

How seriously a diagnosis of tertiary syphilis of the lung need be considered when a patient with nasal pulmonary signs has other stigmata of the disease or a positive Wassermann reaction is an undecided question. Although in our experience tracheobronchial syphilis has been encountered many times, syphilitic disease of the parenchyma of the lung has been diagnosed but once positively and only on two other occasions with reasonable probability. When one recalls that only twelve instances were found in an analysis of 2,500 autopsies at the Johns Hopkins Hospital, in no case among 4,700 postmortem examinations at the Massachusetts General Hospital and that only twelve cases were discovered some years ago in the Museums of London, he must be impressed with the rarity with which acquired syphilis affects the pulmonary tissue, and to marvel how even by following his admonition "always to think of the possibility of syphilis" Dieulafoy was able to recognize six different types of luetic involvement of the lungs.

The mere association of the signs of pulmonary infection with a positive Wassermann does not establish the etiology of the former; however, if, after the administration of antiluetic treatment to an individual who has a history of syphilis, a positive Wassermann reaction or perhaps a proliferative periostitis or signs of old interstitial keratitis, of aortitis or of orchitis, the evidences of pulmonary disease disappear, the presumption is strong that the latter was of syphilitic origin also. But for proof to be conclusive even in such cases, examinations of the sputum or of the bronchial secretion should have been made to exclude the presence of treponemata other than the *treponema pallidum*, *spirilla*, *fusiform bacilli* and *vibrios*,

infections which are influenced favorably by the same drugs that are employed in the treatment of syphilis.

So-called primary chronic pneumonia spoken of in the older literature and described well by Wagner, by Aufrecht, Frankel and others is a clinical syndrome with a chronic relapsing course, a slow, progressive spread of definite consolidation until it may involve one or more lobes of a lung and a termination at times in pulmonary suppuration. This must be a rare condition and it may be doubted with propriety whether or not a chronic pneumonia in the true sense occurs at all.

After the foregoing conditions have been excluded as the cause of the symptoms of chronic bronchopulmonary disease, the treatment of the respiratory infection may be instituted.

Although perhaps some of these chronic non-tuberculous infections may regress after relatively simple forms of treatment, the majority of them are resistant to the measures utilized generally. For that reason if for no other, every effort should be made to prevent the development of them. Prophylaxis so far as we know at present should be directed toward the prevention or the prompt and adequate treatment of infections of the tonsils, the paranasal sinuses and of the buccal cavity, especially the gums, so as to minimize the likelihood of an extension of the infection to the lower respiratory tract. The avoidance of living or of working in dusty surroundings and the institution of good hygienic habits with adequate diet, sunlight, fresh air and recreation, are additional measures indicated in the case of every patient who has what seems to be merely a subacute or a chronic bronchitis for which no cause is found readily.

In some cases, in addition to the foregoing, residence in a dry, warm, equable climate has been followed by an amelioration of the symptoms. The elimination of all loci of infection in the upper respiratory tract and in the mouth has been helpful in treatment as in prophylaxis, and several patients have been observed whose symptoms and signs regressed completely after a pansinusitis had been cured. Inhalations of steam or of other volatilized medicaments and the oral administration of drugs of the creosote and opium group may be followed by symptomatic relief, but although many modes of treating the established syndrome with productive cough have been utilized, until recently that of postural drainage

advocated by Garvin was followed by the most satisfactory results. With this procedure the attempt is made mechanically to promote drainage of the secretion from the bronchi by means of gravity. The patient assumes an inverted or a semi-inverted position such as the Trendelenburg position with the face up or down or may bend over the edge of a bed, table or chair with his head toward the floor. An individual will gradually acquire the ability to maintain this attitude for some time without discomfort and he should be encouraged to do so for at least fifteen minutes three or four times during the day. This may be helpful even to those who have very little sputum. Now and again, brief febrile reactions with constitutional symptoms follow the treatments. Our experience with the repeated drainage of secretion through the bronchoscope has been too limited to estimate the value of the method but theoretically there is much to sanction a test of it.

A number of patients have been treated with injections of vaccine made from cultures of bacteria that were isolated from the washed sputum but the results in our clinic have been disappointing. However, it may be as Jackson has suggested that autogenous vaccine made from the mixed flora grown from secretion obtained directly from the bronchi through a bronchoscope will be more efficacious.

If examination of the secretion in the bronchi discloses the presence of spirochetes, spirilla or fusiform bacilli, 0.4 gms. of sulpharsphenamin dissolved in ten cubic centimeters of distilled water introduced through a bronchoscope and a like dose given into a vein several times weekly has been followed in some cases by good results.

Should symptoms persist, after any or all of the foregoing measures have been tried, it is unwise indefinitely to await a subsidence of the infection, for prolonged temporizing may lead to increased structural damage and perhaps to the development of a localized or a generalized bronchiectasis. To prevent such an unfavorable consequence, it seems advisable in selected individuals to induce relaxation or a partial collapse of the affected lung in an attempt to increase the drainage of the focus of infection and to limit the mobility of the diseased area and thus to promote slowing of the local circulation and the formation of fibrous tissue. Of the several

methods available to accomplish this end, that which produces a paralysis of the phrenic nerve has seemed to be the one adapted best to meet the indications in this group of patients. It is preferable to artificial pneumothorax for induction of the latter will be impossible in many patients because of the presence of an adhesive or an obliterative pleurisy and because of the necessity when it can be done successfully repeatedly to introduce air into the thorax with the attendant risk of infection and of exudation. Whether the nerve shall be injected with alcohol, evulsed, crushed or a portion of it be excised may be a matter of individual preference. However, the function of the nerve is abolished, relaxation and therefore elevation of the corresponding leaflet of the diaphragm is brought about with a consequent diminution of the volume of the hemithorax, and of the contained lung. Not only is the lung relaxed in this way, but it is actually compressed somewhat especially during the expiratory stage of the tussive effort and the secretion in the infected area is expelled more readily. The peripheral part of the lower lobe is affected most often in the group of cases discussed and inasmuch as this is the site compressed most effectually when the diaphragm is paralyzed, the production of a phrenic palsy on the diseased side is a rational therapeutic procedure.

In a small series of patients with unilateral basal pulmonary infections with evidences of a developing bronchiectasis, paralysis of the homolateral half of the diaphragm produced by excision of a part of the cervical portion of the phrenic nerve has been followed by very evident clinical improvement. Our little experience does not justify more than very tentative conclusions. Promptly after the operation the output of sputum decreased from as much as ninety cubic centimeters daily to ten cubic centimeters or less even though the râles audible in the dislocated lower lobe were not decreased for several days or even weeks. No symptoms of retained secretion—fever, malaise, tachycardia, *etc.*—developed and the general health improved. What the later effect upon the evolution of the pathologic process will be, further observation will show, but the change in the status of these patients thus far gives promise of a better outcome of the infection than has been observed in those treated by the older accredited methods.

Perhaps in certain cases when a phrenicectomy has been ineffi-

cacious, pneumothorax may be helpful and the former procedure may so relax pleural adhesions as to make possible the induction of a degree of pneumothorax that could not have been brought about otherwise.

Let it be emphasized that neither of these more radical procedures should be employed until the more conservative ones have proved ineffectual or unless there are signs of beginning bronchiectasis.

In short, there is a type of chronic inflammation of the bronchopulmonary mechanism that tends with considerable regularity to be limited to the inferior parts of it.

No strictly specific etiology has been demonstrated, but there is reason to think that in addition to the flora concerned in the causation of pulmonary suppuration in general, streptococci, pneumococci and influenza bacilli may be important factors.

Now and again, bronchiectasis develops at the site or sites of the chronic inflammatory changes, but whether because the primary disease created the anatomic foundation for the subsequent dilatation of the bronchial arborizations, or because from the very first the condition was in reality an incipient bronchiectasis, is not known.

It is suggested that if the usual methods of treatment fail to arrest the symptoms and to eradicate the infection within a reasonable period of time, the induction of a phrenic paralysis in chosen cases, supplemented or not by an artificial pneumothorax, may prevent the evolution into bronchiectasis or be a beneficial form of therapy if that untoward sequel has developed.

THE SEQUENCE OF EVENTS IN THE DEVELOPMENT OF CLINICAL PULMONARY TUBERCULOSIS

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So much has been written about clinical tuberculosis in recent years that it is only now and then that one can offer a new explanation for some previously observed phenomenon, or give expression to well-recognized phases of the disease with any degree of individuality, yet I am going to attempt a discussion of the events and their sequence in the development of clinical tuberculosis in a manner which may differ somewhat from the usual description.

Primary Infection.—It is inconceivable that any one could pass through life without coming in contact with tubercle bacilli. It is further inconceivable that many should escape infection and its consequent specific protection or destruction.

The question whether or not histologic tubercle is necessary in order to awaken specific resistance in the host is almost universally answered in the affirmative, yet one may speculate as to the possibility of bacilli being taken into the body and being destroyed and setting free bacillary substances in quantities sufficient to stimulate and sensitize the cells, and sharpen the defense in the absence of infection. In this connection it is generally recognized that dead bacilli, when injected into an animal, will arouse the mechanism of specific defense; and it is further known that tuberculo-protein is able to increase a specific defense when once established.^{1, 2}

This subject has been approached by Zinsser and Mueller³ who cite the works of Bail,⁴ McJunkin,⁵ and Lange,⁶ and give some inconclusive yet very suggestive experimental data which show that tissue filtrates of tuberculous lesions when injected into guinea-pigs may cause substances to be thrown into the blood which will sensitize a second guinea-pig to tuberculin, the reaction appearing within a few days.

Primary infection is responsible for establishing an increased resistance to bacilli which proves to be deterrent to further success-

ful implantations, yet, in instances in which complete healing fails to take place, this focus furnishes a source of bacilli for future reinfection. All of the phenomena of primary infection may take place without any recognizable signs on the part of the host.

Reinoculation.—It is not until the primary infection has spread from its first localization or until reinoculation from without has taken place that the phenomena of disease present themselves. The body cells react more or less vigorously to reinoculations according to the degree of sensitization which has been brought about by the primary infection, and the numbers and virulence of the bacilli causing the reinfection. In this connection metastases from the primary focus must be looked upon as reinoculations if they occur after specific defense has been established, otherwise as multiple primary foci. The effect of such further infection coming on after the primary focus has been established will differ according to the degree of immunity that has been built up.

It is the local allergic reaction which takes place between sensitized cells and bacilli and bacillary protein at the point of reinfection that starts the chain of symptoms and signs which characterize clinical tuberculosis.

Allergy.—One cannot understand any of the phases of clinical tuberculosis apart from the allergic reaction, for they are all due directly or indirectly to it. Its pathology, both anatomic and physiologic; its symptomatology; the phenomena by which it is detected by physical examination, X-ray and the tuberculin test; its confirmation by bacilli in the sputum; and its treatment, whether successful or unsuccessful, are all connected with allergy. Fig. 1 shows in the lung, accompanied by an allergic exudative reaction of marked an infiltration in the lung, accompanied by an allergic exudative reaction of marked degree. Fig. 2 shows an infiltration of the preponderantly proliferative type, in which there is a maximum of exudation.

Tuberculoallergy may be described as that quickened and heightened inflammatory response which takes place in one who has previously been inoculated by living tubercle bacilli or dead bacillary substance, whenever bacilli or bacillary protein are again brought into contact with his cells.

The intensity of this allergic reaction depends upon factors

associated both with the previous infection and the reinfection. Being sensitized, the cells are rendered hypersusceptible to the presence of tubercle bacilli and bacillary protein; and at first may react quite violently to very small dosage. Repeated reinoculations, however, are responsible up to a certain point in the immunity response for increasing the capacity of the cells to withstand further inoculations of bacilli or bacillary protein without severe reaction; for later in the course of the disease the patient may respond with mild reaction only, to many times the numbers of tubercle bacilli and many times the amount of tuberculo-protein which was required to produce violent inflammatory response and probably destruction of tissue earlier in the course of the infection.

This increased capacity of the cells to withstand larger and larger doses of tuberculo-protein is a fundamental necessity if the host is to be successful in overcoming tuberculosis. Were it not for this fact no patient could recover from an extensive disease. In fact, if the cells should continue to be as sensitive during the after-course of the disease as they are when they react to the first reinoculation of any considerable numbers of bacilli with severe exudative inflammation with or without cavity formation, no patient could ever hope to live long after the early extensions of the disease had taken place.

The Allergic Reaction and Specific Defense.—There is much confusion in the minds of medical men as to the nature of allergy and as to its relation to immunity.

That allergy is associated with the reaction of the body to a reinoculation of bacilli or bacillary protein is universally admitted; but writers differ greatly in the properties which they assign to it. Some believe it is primarily protective and that its power to do injury is secondary; others believe that it is an injurious reaction to be avoided; and still others look upon it as a defensive reaction, necessary to protect the host until he builds up a high degree of specific defense, after which the allergic response grows less and less necessary. All admit, however, that it has power of doing injury to the tissues when excessive.

One can make no progress in the interpretation of clinical tuberculosis without recognizing as a fundamental characteristic of the allergic reaction that a small number of bacilli or a small amount of tuberculo-protein will produce a much more violent response early

in the disease than greater numbers of bacilli and larger quantities of tuberculo-protein will later. A patient may show symptoms which are more marked when the lesion is comparatively small than when it is more extensive.

The violent reaction of allergy confined as it is to areas of infection and reinfection must be looked upon as the necessary response of the host to the particular amount of infection at the time. I cannot interpret it in any other way. It undoubtedly concentrates the protective phenomena at the place where they are needed; and particularly in the early stages of the disease before the patient's ability to withstand large doses of bacilli have been developed to the degree that they are later, it even goes to the point of destroying the tissues if necessary in order to remove large masses of bacilli from the body and protect the patient from the necessity of destroying them, which he might not be able to do; or in case of failure, of having them scattered through his tissues to produce new infection.

It is one of the first principles in therapy to always keep the requirements of the allergic reaction below the point of tissue destruction if possible. This is done by avoiding those things which tend to cause massive reinoculation and widespread dissemination of the disease.

Each inoculation and reinoculation successfully combated increases the patient's ability to cope with bacilli until finally a very high state of specific resistance is attained. Whereas a few bacilli gaining access to the tissues through the air passages will cause infection in a non-immune individual, as I have frequently pointed out, the patient suffering from advanced tuberculosis will often cast out millions of bacilli per day which pass over his mucous membranes without causing new implantation. This can be interpreted only as showing that there is some change wrought in the cells of the bronchi of infected individuals which makes them resistant to the entrance of bacilli.

Again, I have called attention to the fact that the patient may react with less violence when the lesion is long existent and extensive than when it is recent and small; and further, that cavity may form early in the disease, but that cavitation rarely continues in the sense of one big cavity forming after another, no matter if the lesion keeps on spreading. The cells seem to attain a certain degree of

protection from the destructive allergic response which manifests itself early. It seems to gain this protection, too, as a result of infections which have gone before.

The body's response to these reinoculations is both anatomic and physiologic. The symptoms are physiologic and indicate in what manner the normal workings of the human machine are disturbed. We compare the symptoms with the anatomic changes present and arrive at a diagnosis and also gain understanding of the mildness or seriousness of the disease process.

Chronology of Early Events in Tuberculous Disease.—Something like the following is the chronology of early events in tuberculous disease:

(1) A reinoculation takes place in an individual whose tissues have been sensitized by previous infection.

(2) As a result of the sensitization the tissues react allergically to the new bacilli, producing, according to the numbers and virulence of the infecting bacilli and the degree of sensitization of the cells, a hyperemia; an exudation of a few cells; an exudation of serum, cells and fibrin into the tissues and air spaces; or a destruction of tissue with cavity formation. Tubercle formation is a secondary reaction in cases of reinoculation.

(3) As the bacillary protein and the protein from destroyed tissue cells is set free it is split into various products some of which are toxic. These gain access to the circulation and produce systemic effects which result in a definite group of symptoms which are known as "general," "systemic," or more appropriately "toxic" symptoms.

(4) The effect of allergy is probably primarily to defend against invasion, and secondarily to facilitate repair of injury which might result from the infection. It produces an inflammatory reaction in the lung which irritates sensory neurons which in turn carry the stimuli to the central nervous system and there transfer them to outgoing neurons which produce reactions in other tissues, causing a large group of "reflex symptoms."

(5) The allergic response further causes certain local structural changes which produce effects immediately at the site of the reaction, the so-called "local symptoms," or the "symptoms due to the tuberculous process *per se*."

(6) The local structural changes, that is, the infiltration and exudation in the tissues and the loss of tissue, produce effects which may be detected on inspection, palpation, percussion, and auscultation, and which further may be visualized by an X-ray film.

Method of Onset of the Disease.—Our conception of what occurs in this early phase of the disease when it is assuming clinical proportions is something like the following. Comparatively small reinoculations take place at first and raise the sensitiveness of the cells toward tuberculoprotein so that a larger reinoculation will be opposed by severe reaction. This reaction consists of many factors, some known and others unknown. That the capacity of the body to cope with greater and greater numbers of bacilli is increased as a result of them is generally recognized. Bacillary destruction is stimulated, humoral antibodies are increased according to many workers, the bacilli are checked in their progress through the tissues and if the numbers of bacilli are too great at any one focus, caseation and destruction of the focus take place through which they are eliminated. So, the first phase of specific defense seems to consist of a more energetic response than is required later; in fact, later the defense seems to be much more effective although accompanied by phenomena of milder reaction.

There are several ways in which tuberculosis advances to the point where it assumes the proportions of a disease:

(1) Slowly: the reinoculation being caused by few bacilli, and these probably of low virulence. This type does not put the allergic defense to any severe test, it does not call out any violent response, and results in a preponderantly proliferative process; and, when it eventually produces symptoms, does so either because of the extent of the lesion or because it has finally assumed characteristics of greater acuteness.

(2) More rapidly: the reinoculation being caused by larger numbers of bacilli and probably of greater virulence, and successive reinoculations coming on with greater rapidity. This type shows greater allergic response. A few foci may liberate sufficient bacillary protein to diffuse through and cause exudative phenomena in areas somewhat distant from the areas of infection. It is characterized by a marked activity and causes symptoms with a comparatively small area of involvement.

(3) *Acutely*: a large reinoculation with relatively virulent bacilli takes place at a time when the cells are highly sensitized. The result is a violent allergic response which causes a more or less widespread inflammation with or without extensive destruction of tissue. Rapid cavitation with elimination of many of the bacilli, and an open pathway to the outside world for those that remain is a common result of this type of onset.

Etiologic Classification of Symptoms.—In the chronology of events which accompany the onset of the disease, three groups of symptoms were mentioned, each being due to a distinct and particular cause:^{7, 8, 9, 10, 11} (1) the “toxic group”; (2) the “reflex group”; and (3) “symptoms due to the tuberculous process *per se*.”

This classification gives an understanding of what is taking place. There are many symptoms caused by tuberculosis, but they will one and all fall into one or the other of these three groups. The simplicity and value of this classification must appeal to the student of physiologic medicine. Its value is further enhanced by the fact that the same classification may be used for infections in other organs.

1. *Toxic Group of Symptoms.*—Toxins have a widespread action and probably, directly and indirectly, affect all of the cells of the body, lessening the efficiency of their action. The action of all toxins is qualitatively similar, but quantitatively dissimilar. They produce many of the characteristic effects of the major and minor emotions. They result in a widespread nerve imbalance similar to that observed in so-called neurasthenia, or in endocrine disturbances, or those which characterize psychasthenia. Many of the symptoms of toxemia are expressed in tissues and organs in which we are able to study them carefully such as the heart, blood-vessels, respiratory system, gastrointestinal system and dermal structures. From the visceroneurological standpoint they may be classed predominantly as sympathetic effects. Thus the heart-beat is accelerated; the blood-vessels are constricted; the secretions of the respiratory tract often seem to be reduced; respiration is hastened; the secretion of the gastrointestinal glands is diminished and the contraction of the musculature is inhibited; and the pilomotor, sweat and vasomotors of the skin are activated. The sympathicotrophic glands of internal secretion, particularly the adrenals, thyroid and pituitary, seem to

be stimulated to increased activity by acute toxemia; and to hypoactivity in case of long-continued toxic action.

The following are the common toxic symptoms of tuberculosis, together with the suggested manner of their production.

GROUP I

SYMPTOMS OF TOXEMIA

<i>Caused by Harmful Stimulation of</i>	<i>Symptoms</i>
I. Body Cells Generally	1. Malaise
II. Nervous System Generally	2. Lack of endurance
III. Endocrine System Generally	3. Loss of strength
	4. Nerve instability
	5. Diminished digestive activity
	6. Increased metabolic rate
IV. Sympathetic Nervous System	7. Loss of weight
V. Sympathicotropic Endocrines	8. Increased pulse rate
particularly adrenals and thyroid	9. Night sweats
	10. Temperature
	11. Anemia
	12. Leukocytosis

2. *The Reflex Group of Symptoms.*—The lung, being innervated by both sympathetic and parasympathetic (vagus) nerves, has the afferent nerves which course with both of these systems as agents for originating reflexes. These two systems furnish afferent components for some forty reflexes, as I have discussed elsewhere.^{11, 12, 13}

There are certain irregularities in the reflexes from the lung when compared with those from other important viscera, which should be discussed. This is shown in the somatic reflexes. Instead of joining with spinal nerves to form reflexes in the upper five or six thoracic segments of the cord, in the same levels which the impulses that are carried over the afferents of the sympathetic system of the lung enter, they join with efferent spinal nerves in the third to fifth cervical segments. This can be explained, however, on the basis that the lung arises developmentally, along with the diaphragm, from this portion of the cord.

I have suggested that the impulses which produce the somatic reflexes from the lung enter the upper thoracic portion of the cord over the sympathetic (spinal) afferent system, and are then transferred upward over intracentral paths to join with the midcervical

nerves to form the reflexes. Rasmussen on account of the paucity of sympathetic fibers found in the lung by Larsell, has suggested that these reflexes might be caused by the impulses being carried over the vagus and then transmitted downward to the midcervical segments. Since all other important viscera when inflamed produce somatic reflexes which are formed regularly by the mediation of impulses transferred centrally over the afferents of the sympathetic system and the efferent spinal nerves, and all of these follow the developmental relationships in the cord it seems equally or more probable that the irregularity in expressing the reflex would be in the afferent component of the reflex. All such organs as the heart,

GROUP II

REFLEX SYMPTOMS FROM THE LUNG

<i>Afferent Nerves</i>	<i>Symptoms</i>	<i>Efferent Nerves</i>
Inflammation of Lung	Hoarseness..... Laryngeal irritation..... Cough..... Cough.....	Laryngeal nerves. Superior laryngeal nerve. Laryngeal and nerves to all expiratory muscles with inhibition of nerves to inspiratory muscles.
	Inhibition of heart..... Increased muscle tonus and glandular secretion in gas- triontestinal canal..... Flushing of face..... Spasm of sternocleidomas- toideus and trapezius..... Deviation of tongue from median line..... Degeneration of facial mus- cles.....	Motor fibers of cardiac vagus. Motor fibers of gastric and intestinal parasympathetic. Sensory fibers of Trigemimus. Spinal accessorius. Hypoglossus. Trigemimus and Facialis.
	Flushing of ear..... Dilation of pupil.....	Third sensory cervical. Motor from Budge's Center (lower cervical and upper dorsal).
	Spasm of muscles of shoulder girdle and diaphragm..... Lessened motion of chest wall, partly due to muscle spasm as above..... Pain above 2d rib and spine of scapulae (superficial)...	Cervical motor nerves, IId to VIIIth. Cervical motor nerves, IId to VIIIth.
	Pain in muscles of shoulder girdle (deep pain)..... Degeneration of skin and subcutaneous tissue above 2d rib anteriorly and spine of scapulae..... Degeneration of muscles of shoulder girdle.....	Cervical sensory nerves, par- ticularly IIIth, IVth, and Vth. Cervical sensory nerves, IId to VIIIth. Cervical sensory nerves, IIIId, IVth and Vth. Cervical sensory and motor IId to VIIIth.

liver, pancreas, stomach, intestines and kidney, when inflamed, produce reflexes regularly in skeletal nerves which emerge from the same segments that receive the impulses over the afferent sympathetic system, while the vagal reflex effects are restricted regularly to the cranial nerves.

If the suggestion of Rasmussen is correct, then the lung proves to be an exception to all of the important organs in not having reflexes which originate in the sympathetic afferent system, which seems hardly probable when it has a sympathetic system.

The table on page 135 shows many of the common reflex symptoms which are met in pulmonary tuberculosis, together with the probable afferent and efferent paths through which they are produced.

3. *Symptoms Due to the Tuberculous Process per se.*—There is one syndrome and three symptoms which are caused directly by the tuberculous process, as follows:

GROUP III

SYMPTOMS DUE TO THE TUBERCULOUS PROCESS *Per Se*

"Colds" (tuberculous bronchitis)

Spitting of blood

Pleurisy (tuberculosis of pleura)

Sputum

Marked immunity responses to fairly large reinoculations of bacilli produce a tuberculous bronchitis with toxic symptoms, cough, sputum, and reflexes in the larynx. The same symptoms are apt to follow whether the infection results in infiltration only, or in infiltration and cavitation. The patient usually speaks of this reaction as a "cold." This is strictly a syndrome comprised of symptoms found in all groups, but its local origin may justify its classification in Group III.

When the allergic reaction results in caseation and necrosis it is responsible for the expulsion of tubercle bacilli from the lung, in which case bacilli may be found in the sputum.

Failing necrosis and the rupture of tubercles into the air passages, the inflammation may still be accompanied by sputum due to a local increase in bronchial secretion. This secretion sometimes contains an increased number of lymphocytes when it is of tuberculous origin, even though bacilli are not found.

It is a recognized fact that vessels which participate in inflammation are dilated. Their walls are more permeable than normal and so at times they allow red blood-cells as well as other constituents of the blood to pass through, causing hemoptysis. Hemoptysis may also be caused by direct injury to vessels.

If the inflammation underlies the pleura, close to its surface, then pleural pain or effusion may be present.

These local effects are the most significant of all symptoms caused by pulmonary tuberculosis. They are definitely localized in the lung.

The Allergic Reaction and Physical Signs.—Tuberculous disease makes its presence known both by disturbances in physiologic action, and by anatomical change. This change in structure, too, is a result of the allergic reaction.^{2, 14, 15, 16}

Allergic reaction as it manifests itself directly and indirectly in structure alteration is the basis of most of the findings which are revealed by physical examination and the X-ray.

Through inspection we are able to determine the physiologic disturbance in respiratory motion which is produced by the reflex contraction of the apical muscles (the sternocleidomastoideus, subclavius and scaleni) which connect the upper ribs and sternum with the cervical vertebrae above; and, the contraction of the crus and central tendon of the diaphragm below. The contraction of these muscles limits the motion of the hemothorax on the side of the involvement causing so-called "lagging of the side," a very important symptom of pulmonary inflammation when properly interpreted.

Aside from this, the changes in the structure of the muscles, particularly the sternocleidomastoideus, scaleni, pectorales, trapezius, levator anguli scapulae and rhomboidei, in the form of increased tension may often be evident to the eye when the disease in the lung is active; and degeneration of these same muscles and the skin and subcutaneous tissue between the second rib and angle of the jaw anteriorly and the spine of the scapulae and the base of the skull posteriorly may be readily seen when a tuberculous lesion has existed for a long time. Likewise, degeneration of the skin and subcutaneous tissue below the second rib and spine of the scapula tells the eye in unmistakable language that the underlying pleura has been long involved in inflammation.

Through *palpation* we are able better to determine the spasm and degeneration of the muscles and the degeneration of the skin and soft tissue than we are by inspection. Through inspection and palpation of these soft tissues one may not only obtain information concerning the presence of pulmonary tuberculosis, but he may judge as to whether or not it is active or healed and obsolete at the time of examination.

Through palpation one may also determine the differences in density which mark different pathologic processes such as infiltration, cavitation, emphysema, pleural effusion and pneumothorax. Even the differences between severe exudative allergic reactions and mild allergic responses may be appreciated.

It is the allergic reaction in the form of exudation in the tissues, or the fibrosis which has been formed in response to it, or the destruction and excavation which has resulted from it, that we are attempting to detect by *percussion*. The major changes, whether infiltration, exudative or proliferative; excavation; or accompanying emphysema, all result directly or indirectly from the body's allergic response to reinfection or inoculations of tuberculo-protein.

So is it, too, with *auscultation*. We are attempting to discover changes in the tissues as they react to the bacilli and bacillary protein. The signs found on auscultation, whether alterations in the respiratory note or rales, vary with the degree of allergic response of the patient. One learns to distinguish the mildness of the dry infiltration of preponderantly proliferative lesions from the moist processes which characterize the preponderantly exudative lesions and which are due to violent allergic response on the part of the host.

The X-ray, too, depends much on allergy. The roentgenologist has learned to translate his shadows in terms of allergy. The soft cottony shadows of exudation are interpreted as meaning the more active lesions and the discrete, well-defined linear shadows are interpreted as being due to fibrosis. So here, too, the ability to determine the character of the active allergic response or the new tissue formed as a result of it are the chief factors in the diagnostic value of this procedure.

SUMMARY

(1) I have attempted to show in this paper how the primary infection sets the immunity mechanism working so that reinoculation is met by an immunity response.

(2) This immunity response is indicated either directly or indirectly by some phase of allergic reaction.

(3) The allergic reaction, being inflammatory in nature, results in both anatomic and physiologic disturbances.

(4) The degree of allergy present varies with the nature of the onset of the disease; being relatively mild when the onset is insidious and relatively marked when the onset is acute. Allergy further determines the course which the disease will follow after it has developed.

(5) The anatomic and physiologic disturbances caused by the immunity response furnish the symptoms and signs upon which the recognition of the disease depends.

(6) The symptoms group themselves about three causes:

(a) *The toxins, which act generally throughout the body.*

(b) *Stimuli which produce reflex effects in other organs and structures through the sympathetic and vagal pulmonary fibers.*

(c) *Local irritating and destructive effects at the site of infection.*

(7) The anatomic changes which result directly and indirectly from the reaction of the patient toward the infecting bacilli and bacillary substances cause the diagnostic phenomena observed on (a) inspection, (b) palpation, (c) percussion, (d) auscultation, (e) through the X-ray, and (f) through the diagnostic application of tuberculin.

(8) Thus the evolution of tuberculosis as a disease is a natural sequence of events based upon the amounts and nature of bacilli and bacillary substances on the one hand, and the nature of the specific defense by which the patient meets them on the other, and the disease picture at any one time represents the patient's immunity response to his disease at that particular time.

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THE DIAGNOSIS OF A FOREIGN BODY IN A BRONCHUS

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IN THE study of this patient we will reverse the usual order, study the physical signs first and then try to work out the condition, or conditions, that might produce them. Then we will go over the history and the findings from methods of examination other than by our own senses. This is what you will have to do when you see patients who are delirious or unconscious and about whom you have no history. Such an order of study gives you more respect for the veterinarian, who has to depend so much on observation. The students who are to examine the patient have not seen him before. The patient is J.A., aged eight years, admitted March 11, 1931.

Examination.—*Mr. A.* The boy is well nourished and comfortable, flat in bed. His color is good and he shows no signs of any dyspnea or cyanosis. The examination of the eyes and mouth shows no abnormal condition.

Mr. B. The thorax is well formed and slightly asymmetrical, the left side being rather fuller. There is distinctly less expansion on the right side, most marked below. There is some movement of the diaphragm on the right side. The vocal fremitus is well marked over the left side and upper right thorax but is decreased over the lower right chest.

Dr. McCrae. Be sure of your observation as to vocal fremitus and try to determine over what area the fremitus is decreased.

Mr. B. Some fremitus is undoubtedly felt and the area over which it is decreased corresponds to the middle and lower lobes.

Mr. C. The percussion note is resonant over the left side and upper right thorax. There is dulness of some grade over the middle and lower lobes. It is not of extreme grade. There is not any great increase in the sense of resistance.

Mr. A. The breath sounds are well heard over the left side, perhaps slightly harsher than normal. No râles are made out. The breath sounds are much the same over the upper right lobe but

rougher than over the left thorax. Over the area of dulness the breath sounds are heard everywhere. They are not as loud as elsewhere, but are more blowing and have a somewhat higher pitch. No râles are heard. The voice sounds are heard but are rather diminished.

Dr. McCrae. Have you enough evidence to arrive at an opinion of the changes that cause these signs?

Student. Thickened pleura.

Dr. McCrae. In some ways this may be suggested, but you have noted that the signs correspond very closely to the middle and lower right lobes. It is unusual for thickening of the pleura to correspond so accurately to a lobar distribution, although possible. We keep it in mind as a possibility. Is there any other suggestion?

Student. Pneumonia.

Dr. McCrae. Do you suggest lobar or bronchopneumonia?

Student. With involvement of two lobes and the left side clear, it would have to be lobar pneumonia.

Dr. McCrae. Mr. B., how do you regard this suggestion?

Student. It does not seem probable. His temperature is normal and he has no evident dyspnea. If it is pneumonia the signs are not typical. It might be a clearing pneumonia with obstruction of a bronchus by secretion.

Dr. McCrae. These are important objections. In addition we would probably hear some râles if it is a resolving pneumonia. Is there anything else to consider?

Student. Fluid in the pleural cavity.

Dr. McCrae. Mr. A., what is your answer to this suggestion?

Student. The vocal fremitus and breath sounds would be absent and the dulness would be more marked.

Dr. McCrae. Anything else?

Student. There should be shifting dulness, the heart should be displaced to the left and a paravertebral triangle of dulness might be found.

Dr. McCrae. Try to decide these points.

Student. There is no evidence of shifting dulness. The heart seems to be displaced to the right, although not very much, and there is no area of paravertebral dulness.

Dr. McCrae. You are correct. The heart is displaced to the

right, unless it be that he has naturally a centrally placed heart. We can regard fluid in the pleural cavity as ruled out. Is there any other suggestion?

Student. New growth.

Dr. McCrae. A wise suggestion in any puzzling thoracic condition. Do you mean new growth of the lung or bronchus or in the mediastinum?

Student. In the lung.

Dr. McCrae. It would be unlikely at his age. The signs do not suggest any extensive involvement of lung tissue. How might a mediastinal growth produce these signs?

Student. By pressure on a bronchus.

Dr. McCrae. Yes, but in this event there is difficulty in explaining how the bronchus to the upper lobe has escaped unless there has been extension into the lung. As to a new growth of a bronchus, it would be most unusual at this patient's age.

Let us consider a moment if we can decide what physical condition may be responsible for the signs. It does not seem to concern the pleura. The vocal fremitus and breath sounds are decreased but there is evidence that vibrations—usually carried by a column of air—are reaching the lowest part of the affected lung. They are not reaching it as freely as normal.

Student. Some narrowing of the bronchus.

Dr. McCrae. Correct; and what may be responsible for this?

Student. The presence of a foreign body in a bronchus or pressure from without. Something in the wall of the bronchus itself does not seem very probable.

Dr. McCrae. The study of the physical signs suggests that there is some obstruction in the right bronchus below the point at which the upper lobe bronchus is given off. This obstruction is not complete and so far as we can judge from the presence of some air in the middle and lower lobes without any râles at present, there is not much secretion in the lower bronchi.

We will now have the history and find if this aids us in the diagnosis.

The boy complains of cough with loss of appetite and strength. His mother states that he has had fever at times but she does not know the exact figures.

Previous history.—He has had measles, mumps and whooping cough. His tonsils were removed in the summer of 1930 under ether anesthesia. Otherwise his past history is negative.

Dr. McCrae. Mr. B., does this suggest any possibility?

Student. That he may have a lung abscess following the tonsillectomy. Another possibility is bronchiectasis following the whooping cough.

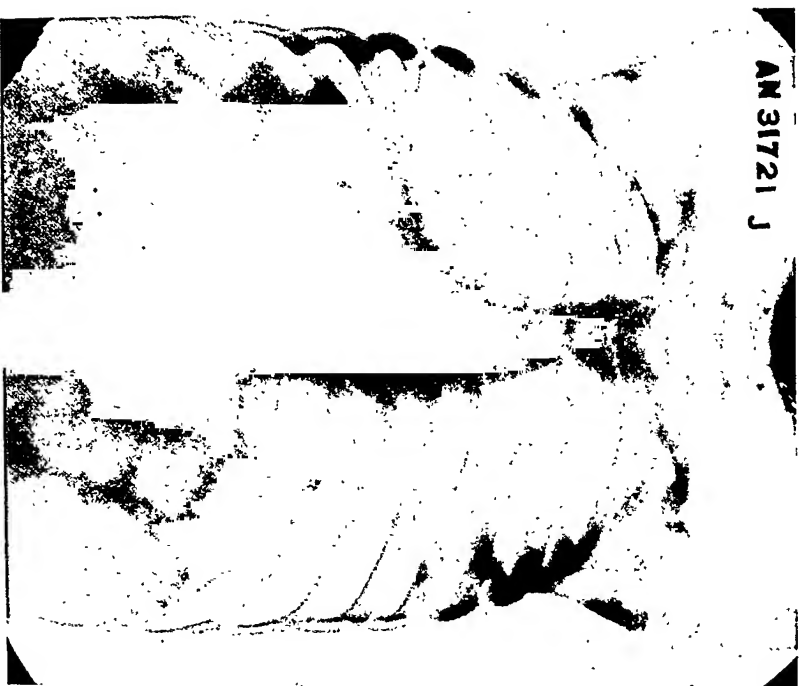
Dr. McCrae. Quite right, but on inquiry we find that he has not had any large amount of sputum, in fact very little, which is against an abscess which has ruptured. With an unruptured abscess we would not expect to have such a large area of dulness over which breath sounds are present. The same points would apply to bronchiectasis. With signs of this extent due to bronchiectasis, there would be larger amounts of sputum. Neither of these seems probable.

Present illness.—On November 27, 1930, he picked up a small rivet, put it in his mouth and began to run. He suddenly had an attack of choking and coughing and found that the rivet had disappeared. He went home, told his mother what had happened, was put to bed and a physician was called. That evening he vomited and the next day he began to cough. After this he spent three weeks in bed, is said to have had fever and pneumonia was suspected. He remained at home until February under the care of a physician. The cough continued, he had fever off and on, and there was a steady loss of weight. He returned to school in February but it was noted that any exertion brought on a severe attack of coughing. Finally he was taken to the Frankford Hospital Dispensary where an X-ray study was made.

The foreign body is shown in Fig. 1. You can see a metallic foreign body, which has one end expanded, in the right bronchus about the level of the middle lobe bronchus. There are considerable changes in the right middle and lower lobes. How much of this is collapse is a question difficult to answer, although the position of the heart is against any marked amount of collapse. With this the heart should be more displaced to the right.

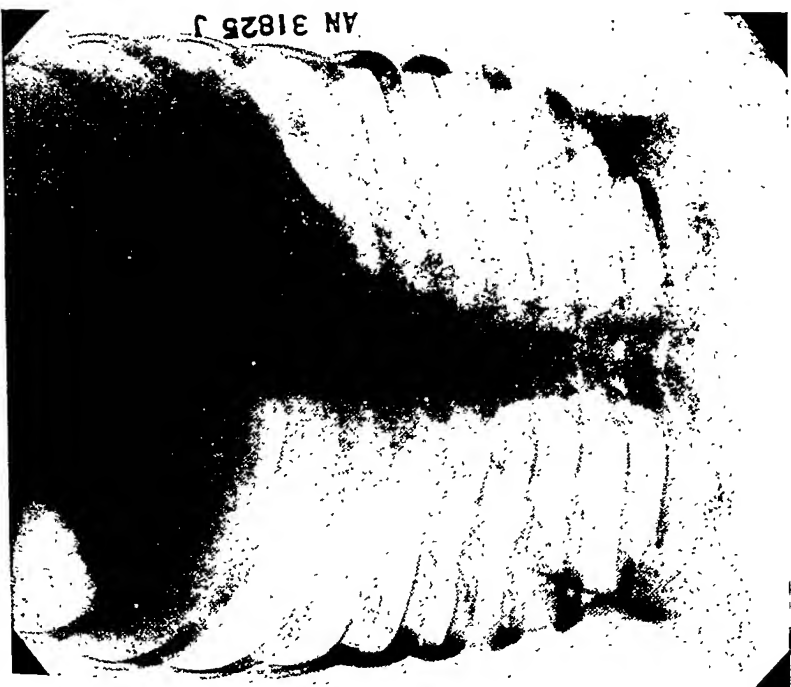
The reason for the signs suggesting some obstruction of the bronchus is now evident, but we have one puzzling point to consider. The foreign body is supposed to be solid. You can see its size and

FIG. 1.



Showing foreign body in lower right main bronchus.

FIG. 2.



After removal of foreign body.

it is evident that it should block the bronchus completely. A foreign body in a bronchus goes down as far as it can. In addition there is swelling of the mucous membrane which aids in making the obstruction complete. Yet from the signs we feel sure that there is not complete obstruction. There are two possible explanations, one that there is a groove in the rivet, the other that it is hollow. It is surprising how small an opening is enough to let some air in and out and keep up some aëration of the affected portion of the lung. In some cases of a hollow foreign body there may be curious sounds heard, usually whistling in character; but there are none such here. It may be noted that there is not any "wheeze" to be heard. While no râles are to be heard at present over the middle and lower lobes of the right side, it is to be noted that a few coarse râles have been heard occasionally, especially after coughing.

I am sure that one question has occurred to us all. Why was this boy allowed to go so long—over three months—with this foreign body unrecognized? The history seems very clear and one would think that the need for deciding as to what became of the rivet would be evident. This applies especially in view of the widespread knowledge of the frequency of foreign bodies in bronchi due largely to the campaign of education carried on by Dr. Chevalier Jackson. It is a curious commentary on human intelligence that this is not an uncommon history among the patients with foreign bodies. In a number of instances there was a perfectly definite history of the foreign body having disappeared, and presumably having been aspirated, but no attention was paid to it. In one instance the child insisted that she had aspirated a foreign body. For this her family laughed at her for several years but finally learned that the child was right.

No one who studies many of these patients can help feeling very greatly impressed by the remarkable carelessness in regard to the history. There is nearly always something that happens at the time of aspiration. This boy had an attack of choking and coughing. In a great many instances this lasts for a short time only and then the patient is comfortable for a time. It is this period of absence of symptoms which often seems to lead to error. It is a safe rule to pay the greatest attention to the slightest suggestion that a foreign body may have been aspirated. In many cases the statements of the

child are brushed aside as of no consequence and unworthy of attention. In other cases it has been supposed that the foreign body must have been swallowed and no more attention is given to the matter. In other cases it has been supposed that the foreign body was too large to have passed through the larynx and no attention was paid to the history. Some day when you are at the College of Physicians, inspect the collection of foreign bodies removed from bronchi by Dr. Chevalier Jackson. You will then realize something of the possibilities.

Another point worthy of mention is that shortly after the aspiration of the foreign body there was a suspicion of *pneumonia*. This occurs very often in the history of these patients. The signs due to the foreign body are very often misinterpreted and a diagnosis of pneumonia is made. My experience is that I have yet to see the first case of pneumonia due to a foreign body in a bronchus. With dyspnea, cyanosis, some fever and thoracic signs, it is easy to make a diagnosis of pneumonia if a careless examination is made. If such an error is made, a few days' observation should correct it, if the patient is carefully examined. The histories often suggest that the diagnosis once made is never reviewed and the error persists.

The diagnosis of *empyema* is another frequent error, probably often born of a previous erroneous diagnosis of pneumonia when the signs do not disappear after a proper interval. This error should not be possible in this boy on account of the physical signs and the position of the heart. Besides the dulness due to empyema does not correspond to a lobar distribution. In cases with complete blocking of a bronchus with the production of the so-called "drowned lung," there may be more excuse for the mistake; but here, too, a careful study should prevent it. In a very few cases empyema follows the presence of a foreign body in a bronchus, usually after some duration, but there is nothing to suggest it here.

The treatment of this condition is removal through the bronchoscope, which will be done this afternoon by Doctor Clerf. We are indebted to him for the opportunity of studying this patient.

The other findings show little of importance. The temperature is normal, the pulse rate averages about 120 and the respirations 30-32.

The bronchoscopic removal was done by Doctor Clerf. There

was a considerable amount of granulation tissue in the right bronchus. Pus was seen coming through the center of the rivet or cylinder, which had a lumen of about 1 millimeter, especially during expiration and cough. The foreign body was removed, the total time required being one minute and fifty seconds. There was no particular disturbance with it.

Subsequent History.—The day after removal, the boy was perfectly comfortable without any dyspnea. The expansion on the right side was less than it was before the foreign body was removed. The other signs were much the same. The reduction in expansion is probably due to the fact that the swelling of the mucous membrane is now interfering more with the passage of air than the foreign body did as it was hollow. This swelling will soon subside.

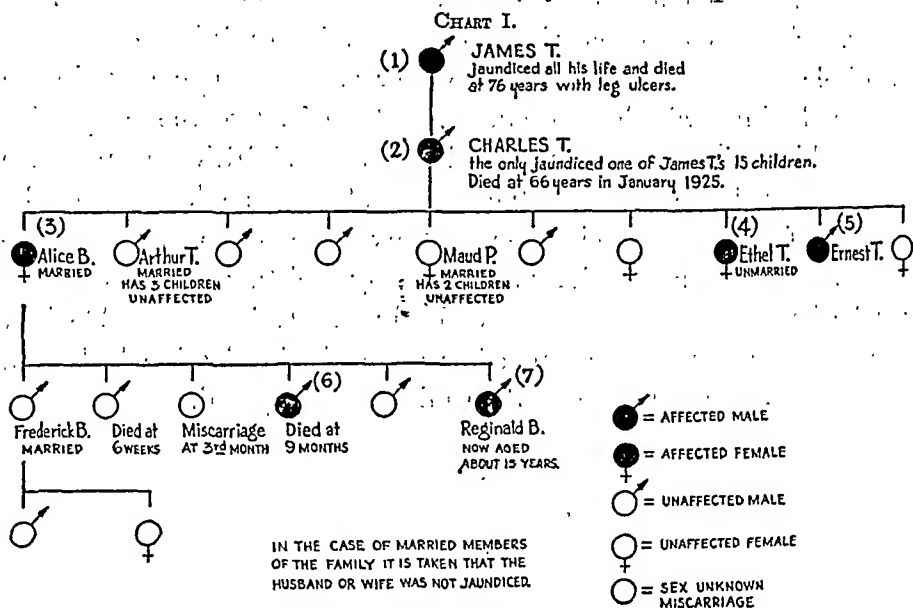
The subsequent history was uneventful and he made a good recovery. Expansion on the right side was still diminished when he was discharged. It is difficult to say how much of the change in the lower right lung will be permanent. There is, too, the possibility of bronchiectasis to consider. Both these possibilities would have been prevented if a prompt diagnosis had been made followed by removal of the rivet. The X-ray study after removal shows improvement in the lung (Fig. 2). You may feel that the chances are that he has permanent damage to the lung. It is remarkable how much improvement may result after removal of a foreign body and the chances are usually better than might be supposed.

A HEMOLYTIC JAUNDICE FAMILY

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IN 1910, with the late Dr. G. Dorner,¹ I described a familial group of cases of congenital hemolytic jaundice, and after many years I have recently come across a (non-affected) member of the family again. Accompanying is a genealogic table of the family up to the present date with the affected members distinguished from the others by the sex-mark being blackened, thus ♂ an affected male, and ♀ an affected female. The husbands and wives of the various married members of the family are not represented on the



Familial group of affected and unaffected male and female members of a hemolytic jaundice family. chart, as it should be understood that none of them had hemolytic jaundice.

It will be noted by a cursory glance at the table that seven members (marked in order of priority) of the family are so far known to have had hemolytic jaundice, but one cannot be quite sure that some of those supposed not to have been affected would not have been found to present very minor symptoms of the congenital-developmental disease had they been carefully examined for that

purpose. Since the present paper, though complete in itself, is to be regarded as a sequel of the former account, I shall not here review the whole symptomatology (most of which is now well known) and nature of the disease, but I will first make some remarks on each of the affected members of the family (in the order of their priority) and then shortly discuss some special points bearing on the subject.

No. 1. James T., the first of the family known to have had chronic jaundice, was yellow all his life, sometimes more so, sometimes less so, and died at the age of seventy-six years (wrongly printed as seventy years in the original account) as the result, it is said, of leg ulcers.

No. 2. Charles T., a son of James T., was the only jaundiced member of his generation of the family. At least one of his sisters and one of his brothers had offspring and they were not jaundiced. He died at the age of sixty-six years (in January, 1925) of pneumonia, and he possibly also had cholelithiasis. When I saw him in 1909, at the age of fifty-three years, he was a moderately jaundiced, but a fairly well-nourished and well-developed man, with a pigmented scar on his right leg. The spleen could be felt three finger-breadths below the costal margin and the liver could be felt just below the ribs, but was not definitely enlarged. Blood count (Prof. A. E. Boycott, Nov. 30, 1909):—hemoglobin 78 per cent.; erythrocytes 3,630,000; leukocytes 8,400 (of which 70.4 per cent. were polymorphonuclear neutrophils). The red cells showed the characteristic anisocytosis, *etc.*, of congenital hemolytic jaundice and two nucleated red cells were seen during the differential count of 500 white cells. The resistance of the red cells towards graduated hypertonic sodium chlorid solutions was greatly below the normal, hemolysis commencing with a 0.75 per cent. sodium chlorid solution. The blood-serum (of an abnormally yellow colour) gave a negative Wassermann reaction. On one occasion during an exacerbation of jaundice the faeces were said to have been pale (? temporary cholelithiasis trouble).

No. 3. Alice B. (married), the eldest daughter of Charles T. (No. 2), when I saw her in 1909, was aged thirty-two years, and was distinctly jaundiced. The spleen could be felt four finger-breadths below the costal margin. The liver was apparently not enlarged.

Blood count (Dr. A. E. Boycott, Nov. 30, 1909): hemoglobin 70 per cent.; erythrocytes 3,520,000; leukocytes 4,750 (of which 78.2 per cent. were polymorphonuclear neutrophiles). Two nucleated red cells were seen in counting 500 white cells. The resistance of the red cells towards graduated hypertonic sodium chlorid solutions was decidedly below the normal, hemolysis commencing with the 0.64 per cent. solution. The blood-serum (of abnormally yellow colour) gave a negative Wassermann reaction. She stated that the jaundice had been accentuated during her pregnancies. Apparently she gets on fairly well without splenectomy, but I have unfortunately not seen her again.

No. 4. Ethel T., sister of No. 3, was aged fourteen years when I saw her in 1909. She was distinctly jaundiced (only very slightly so when seen again in January, 1910), and the lower margin of the spleen could be felt three finger-breadths below the costal margin. The lower edge of the liver could just be felt below the ribs. Blood count (Dr. A. E. Boycott, Nov. 30, 1909): hemoglobin 77 per cent.; erythrocytes 3,460,000; leukocytes 3,800 (of which 77.6 per cent. were polymorphonuclear neutrophiles). Two nucleated red cells were seen in counting 500 white cells. The resistance of the red cells towards graduated hypertonic sodium chlorid solutions was decidedly below the normal, hemolysis commencing with the 0.64 per cent. solution. The blood-serum (of abnormally yellow colour) gave a negative Wassermann reaction.

Through the kindness of Dr. E. Cautley, I saw this patient again in 1916, when she was temporarily in the Metropolitan Hospital, London. She had had an ulcer over the lower part of the right tibia, which she said "came of itself."

Professor Gask kindly informs me that in 1929 she was an in-patient at St. Bartholomew's Hospital under Dr. H. Morley Fletcher when Sir Holburt Waring performed splenectomy on November 13, 1929. She suffered also from cholelithiasis and on March 14, 1930, Sir Holburt Waring performed cholecystectomy. I understand that she is now well.

No. 5. Ernest T., brother of Nos. 3 and 4, was aged twelve years when I saw him in 1909, and was then the least jaundiced of the jaundiced members of his family. The spleen and liver could only just be felt below the ribs. Blood count (Dr. A. E. Boycott,

Nov. 30, 1909): Hemoglobin 69 per cent.; erythrocytes, 3,920,000; leukocytes 10,700 (of which 65 per cent. were polymorphonuclear neutrophils). One neutrophile myelocyte was counted and three nucleated red cells were seen whilst counting 500 white cells. The resistance of the red cells towards graduated hypertonic sodium chlorid solutions was decidedly below the normal, hemolysis commencing with the 0.64 per cent. solution. The blood-serum, as in the other cases, was of abnormally yellow colour and gave a negative Wassermann reaction. In 1909 he had slight enlargement of some of his cervical lymphatic glands and a scar on the neck left by an operation on lymphatic glands.

Some time after heavy artillery work during the War, he was admitted to St. Bartholomew's Hospital, London, with great splenomegaly and severe anemia. I saw him there by the kindness of Dr. J. H. Drysdale, and his spleen was excised by Professor G. E. Gask on January 21, 1921, with the usual satisfactory results.² At the upper pole of the excised spleen there was an area of anemic infarction.³ In June, 1922, Doctor Drysdale told me that the patient had lately had cerebral symptoms—possibly due to thrombotic disturbance. His vermiform appendix was excised in 1927, and some gall-stones were removed.

No. 6. A son of No. 3, was said to have been yellow, and to have died in an anemic condition when nine months old.

No. 7. Reginald B., now (April, 1931) aged about fifteen years, the youngest child of No. 3, is, I understand, definitely a subject of hemolytic jaundice, but I have not seen him.

REMARKS

It was A. Chauffard⁴ who first showed that cases of congenital or familial acholuric ("hemolytic") jaundice (and anemia) could often be recognized by an abnormally low resistance (excessive "fragility") of their red blood-cells towards hypotonic salt solutions, and this discovery led to the correct diagnosis of many cases previously incorrectly classified or half-correctly labelled under various other headings, such as familial Hanot's disease, "familial cholemia," familial splenomegaly, splenomegalic anemia, splenic anemia, Banti's disease, familial hepatic cirrhosis with splenomegaly, *etc.*

However, this abnormal "fragility" of the erythrocytes towards

hypotonic solutions does not explain their fragility within the patient's body, where such "hypotonic" fluids or "juices" can never be encountered. Moreover, though certainly a most useful clinical hematological sign, it is not a constant finding in all cases. It may be absent at times, if not permanently, in more or less affected members of a "congenital hemolytic" family. Thus Gänsslen, Zipperlen and Schütz,⁵ in their great monograph on hemolytic jaundice and the "hemolytic constitution," found that abnormal fragility of the erythrocytes was absent in 10 per cent. of what they called "compensated cases"—quite apart from slight (incomplete) cases.

In apparently "hemolytic" familial cases, recently recorded by Dr. E. A. Cockayne⁶ at the Royal Society of Medicine, there was no abnormal fragility of erythrocytes, and O. Naegeli⁷ admits that this sign may be negative at times, though even in such cases it may become positive under altered conditions, such as in association with the process of compensatory erythrocytosis at high altitudes.

Cases of the congenital hemolytic jaundice group may be divided into: (a) Those in which the main clinical feature is the jaundice, who, according to Chauffard, are "more jaundiced than ill"; (b) those in which the anemia is the "presenting" feature, at all events for the time, and who might be said to be "more anemic than jaundiced" and sometimes are not obviously jaundiced at all, even though their blood-serum is certain to contain more "blood-bilirubin" than the normal maximum (giving a too highly positive indirect Hijmans van den Bergh's reaction); (c) those in which the splenomegaly is for the time the clinical "presenting" sign. When one of these signs is obvious (whether the splenomegaly, the anemia or the jaundice) and when the other signs, if present, have been carelessly overlooked, an error of diagnosis is not unlikely to be made in the absence of hematologic examination and without family history. Obvious clinical jaundice may be absent for years. A case may pass from one to another of these three groups. In typical ordinary cases all three signs are more or less obviously present together. In the present family (family T.) the cases have been fairly typical.

Most observers think that the *fundamental abnormality* is in the red blood-corpuscles, and this fundamental abnormality must, of course, not be confused with the normal appearances connected with

excessive blood-regeneration. By ordinary examination there seems to be microcytosis, but by special examination Naegeli has shown that the apparent "microcytes" compensate (or more than compensate) for the shortness of their maximum diameter by being thicker, that is, of a more globular or spherical shape, than ordinary erythrocytes. It is assumed that some peculiarity of structure must likewise be present that renders them more prone to destruction in the spleen, and so accounts for the usual success of treatment by splenectomy.

One might possibly compare the abnormal inequality in the size of the red cells (anisocytosis), characteristic of hemolytic-jaundice cases, with the inequality of the striped muscle fibres which has been noted in some congenital-developmental muscular dystrophies.

It is not astonishing that with a congenital-developmental abnormality, such as hemolytic jaundice, other congenital-developmental abnormalities may be occasionally associated, but I have not detected any such in the present series. Amongst congenital-developmental abnormalities that have been associated in other familial series "Turmschädel" (turriiform or tower head) has been specially noted by Gänsslen and Naegeli. As I have myself had occasion to observe, some degree of Turmschädel is by no means rare in the region of Tübingen, where Gänsslen made his interesting observations on familial hemolytic jaundice, and it is not surprising, therefore, that both these familial abnormalities should be occasionally associated in the same families of that neighbourhood. Similarly, Curtius and Strempel have recorded the occurrence in one family of two separate remarkable developmental diseases as a result of intermarriage, namely, Recklinghausen's neurofibromatosis and epidermolysis bullosa.⁸

Infantilism, by the way, is very rarely if ever etiologically connected with familial hemolytic jaundice. It was present in a boy whose case I recorded, but there was likewise in him a question of congenital syphilis.⁹ The family history in that case was interesting.

A special tendency to chronic ulceration of the legs has been noted in some hemolytic-jaundice families (H. Batty Shaw, J. W. McNee, Gänsslen, and others). McNee¹⁰ thinks that these leg ulcers are very similar to ordinary varicose ulcers and can easily be healed

by similar treatment. Gänsslen¹¹ writes that the association of leg ulcers with hemolytic jaundice is well known and has been referred to often in the literature by himself and others. In one case to which he has referred a chronic leg ulcer refused to heal under any treatment till splenectomy was performed, after which healing was complete in eight days.¹² In the present familial series (family T.) leg ulcers figure in cases 1, 2, and 4.

The tendency of patients with hemolytic jaundice to suffer from bilirubin gall-stones (as cases No. 4 and No. 5 did in the present T. family series) is now generally acknowledged, the formation of the calculi being apparently favoured by the excessive formation and secretion of bilirubin. The latter is a result of the excessive destruction of erythrocytes in the spleen and to some extent in the reticulo-endothelial tissue elsewhere in the body—probably it is chiefly the peculiar more or less “globular” erythrocytes as described by Naegeli that are prematurely destroyed. The possible prevention of cholelithiasis as a complication furnishes one of the arguments in favour of the performance of splenectomy in these cases relatively early in life.¹³ The possible prevention of severe and dangerous “anemic breakdowns” is likewise a point in favor of operation.

In subjects of hemolytic jaundice the occasional (rare) appearance of actual bilirubin in the urine, independently of the usual excess of urobilin, may perhaps be explained by cholelithiasis, when accompanied by paleness of faeces and increase of jaundice, even in the absence of colic. Abdominal pains in these subjects should not, however, be too readily regarded as due to cholelithiasis. Besides the ordinary causes of abdominal pain, they may be due to perisplenitis or to splenic infarction, which was found to be present in the spleen of No. 5 of this family series (family T.). Exacerbations of jaundice in these subjects are certainly often not connected with cholelithiasis. Increase of jaundice has sometimes been noted in connection with pregnancy, as it was in Case No. 3 of the present family series (family T.).

In conclusion, for purpose of differential diagnosis and contrast, I will shortly refer to an apparently unique case of congenital jaundice which has been for many years under my observation and which apparently belongs to the hemolytic group. It is that of a man (G. T. D.), aged sixty-four years. Excepting for considerable (some-

what variable) jaundice and chronic deafness (due to otosclerosis) and slight nystagmus, he gives the impression of an active, hard-working, hale, elderly man, and has never been seriously ill. He has scars from leg ulcers (left leg) from which he suffered in 1910. It is because he wished to insure his life that in January, 1917, through the kindness of Dr. Otto May, I was first able to examine him. Apart from a very strongly positive indirect Hijmans van den Bergh's reaction for bilirubin in the blood-serum, examination of the blood, urine and viscera shows nothing abnormal. There is no bilirubin or excess of urobilin or urobilinogen in the urine. The osmotic resistance of the erythrocytes is neither higher nor lower than that in ordinary individuals. There is no enlargement of the spleen, liver or superficial lymphatic glands and no xanthoma or cutaneous pruritus. The Wassermann reaction in the blood-serum is negative.

From time to time I have demonstrated the case at the Royal Society of Medicine,¹⁴ but have never seen or heard of any exactly similar case, unless, perhaps, certain doubtful cases of congenital jaundice in adults before the modern methods of examination of the blood and blood-serum had been introduced. I have a note that examination of stained blood-films did not suggest hemolytic jaundice, but further repeated examinations of the erythrocytes might possibly reveal some abnormality in shape, as in the erythrocytes of cases of congenital hemolytic jaundice, according to Naegeli's views. Apparently his jaundice was not passed on to any of his four children (two of them are dead), and no family history of jaundice or anemia can be obtained. In his case the jaundice has been harmless, and there is no evidence that the mere excess of *blood-bilirubin* in the circulating blood (which is the cause of the strongly positive *indirect* Hijmans van den Bergh's reaction in the serum) ever does any harm *per se*.

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TWO CASES OF PRIMARY LIVER-CELL CARCINOMA

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PRIMARY carcinoma of the liver has been the subject of a number of articles since 1876, when Kelsch and Kiener reported two cases. Although these authors were able to find only one other case in the literature at that time,¹ it need not be inferred that its incidence has increased materially in recent years. Rokitsky² thought that carcinoma of the liver "is often a primary affection," and Bamberger³ likewise was of the opinion that carcinoma of the liver is not uncommonly primary, although it occurs much more frequently as a secondary process. It is, nevertheless, comparatively rare. In 29,215 necropsies tabulated by Fox and Bartels⁴ from seven sources, "only thirty-nine revealed primary carcinoma of the liver, an average percentage of 0.133." This corresponds with the statistics reported by Hale White⁵ from Guy's Hospital, London, where twenty-four cases of primary hepatic carcinoma were found in about 18,500 postmortem examinations, a percentage of 0.13. A higher proportion is given by Goldzieher and Bokay,⁶ who found eighteen cases of primary carcinoma of the liver in 6,000 necropsies in a period of five years, a percentage of 0.3. The same percentage is reported by Fried⁷ from the Peter Bent Brigham Hospital, where four primary carcinomas were found in 1,200 necropsies. In 818 consecutive necropsies at the Roper Hospital in Charleston in the last three and a half years, primary hepatic carcinoma was found twice, a percentage of 0.244. If the necropsies of the several preceding years were tabulated, the actual percentage probably would be considerably lower than this. The proportion of primary to secondary carcinoma of the liver is given by Hale White as 1 to 21. Orth⁸ found four cases of primary carcinoma in 258 cases of hepatic carcinoma, or 1 to 64.5.

Histologically, primary carcinomas originate from liver parenchyma or from bile-ducts, the former constituting the hepatomas, to which group the two cases reported in this paper belong.

The primary liver-cell tumors are classified by Ewing as solitary hepatoma, primary massive liver-cell carcinoma, multiple liver-cell carcinoma, and carcinomatous cirrhosis. Cirrhosis occurs in about 87 per cent. of the liver-cell carcinomas and may be present in all forms; but in the rapidly growing multiple carcinomas the cirrhotic change may be absent or very slight. As Ewing⁹ points out, however, there is "no sharp division between this group and solitary massive carcinoma on the one hand, and multiple carcinoma following cirrhosis on the other." Cirrhosis is also present in about 51 per cent. of the bile-duct tumors.

Kaufmann¹⁰ divides the cirrhotic liver tumors into three types: (1) where there is a uniform invasion with multiple circumscribed nodules, (2) where there is a diffuse tumor infiltration, and (3) where there is a combination of types 1 and 2. This group has excited a great deal of interest and there has been considerable discussion as to the relation of the two processes. The arguments in support of the different views need not be set forth here; it is sufficient to say that the general opinion among pathologists seems to be that cirrhosis is the antecedent and exciting factor, the regenerative hyperplasia becoming excessive and neoplastic.

There is a marked tendency in the hepatomas for the tumor cells to invade the veins forming thrombi which sometimes are very extensive, and rapid intrahepatic extension may be brought about in this way. Extrahepatic metastases are less common in the liver-cell type than in the bile-duct type. They occur most frequently in the lungs where the secondary growths are small and as a rule are not recognized clinically. In eighty cases compiled by Fox and Bartels, metastases occurred in 40 per cent., and the lungs were involved in 26.3 per cent.

The diagnosis often presents serious difficulty, especially when the symptoms of a pure portal cirrhosis dominate the clinical picture. In such cases the malignant character may not be suspected before the necropsy; but in other cases the development of an hepatic tumor may terminate the picture of cirrhosis and lead to a correct diagnosis. Primary carcinoma usually runs a more rapid course than secondary carcinoma. Hale White found that among ten patients only two lived as long as four months after the appearance of symptoms, and he thinks that probably the duration rarely ex-

ceeds six months. Of the two cases reported here one lived about three months and one about a month and a half after symptoms were first noticed.

CASE I.—Clinical History.—W. B., a negro man, sixty-five years old, stevedore, entered the Roper Hospital January 23, 1930, complaining of diarrhea and weakness.

Family History.—Unimportant.

Previous History.—Measles, mumps, typhoid fever and smallpox in early life; pneumonia in 1910; influenza in 1919; malaria at various times. Lues and gonorrhea denied. No history of alcoholic addiction.

Present Illness.—Nine weeks before entering the hospital he suffered from looseness of the bowels, the stools at first occurring about a half hour after eating and later increasing to as many as seventeen in twenty-four hours; watery in character. There were generalized intermittent abdominal pains felt especially after eating and described as "cramp-like," more severe in the upper right quadrant and in the epigastrium, partly relieved by bowel movements. He has suffered with nocturia, three to four times, for about three months. The patient's weight when admitted to the hospital was 135 pounds, his average in health being 175 pounds, a loss of forty pounds since the onset of symptoms.

Physical Examination.—The cervical lymph-glands were palpable, but the epitrochlears could not be felt. A slight pulsation of the carotids was noted. The chest wall was thin and expansion rather poor; the percussion note was resonant; the breath sounds vesicular in character but of poor quality; no râles were heard.

Examination of the heart revealed nothing abnormal. The arteries were sclerosed and beaded. Blood-pressure was 125 systolic, 56 diastolic.

Three distinct masses were visible pushing up the abdominal wall, each approximately about the size of a large lemon. Two of these masses were in the epigastrium, one just to the left of the midline, and one to the right and a little lower; the third was in the upper right quadrant three inches below the costal border and just medial to the anterior axillary line. The masses were sensitive to pressure. The liver could be felt six inches below the costal border and extended just beyond the midline to the left; the edge was hard and irregular. The spleen was not palpated. There was a distinct tenderness over the upper abdomen. No jaundice was evident.

Laboratory Examinations.—The urine was of normal specific gravity and showed only a small amount of albumin and a few hyaline casts.

The hemoglobin was 60 per cent. by the Talquist scale; erythrocytes 2,730,000, and leukocytes 9,270; the differential cell count was not significant. Blood Wassermann and Kahn were negative. Urea nitrogen, 26.6 milligrams; blood sugar, 51 milligrams and chlorides, 419 milligrams.

The direct Van den Bergh was negative, delayed direct 2 plus, quantitative indirect 2.9 milligrams.

The faeces were dark brown and contained no blood.

X-ray examination of the gastro-intestinal tract was not very satisfactory, but a large mass was shown, apparently the liver, displacing the stomach to

the left. Examination after inflating the abdomen with gas showed irregularities of the edge of the liver.

A large amount of "moth-ball" infiltration was shown scattered throughout both lungs.

Clinical Diagnosis.—Carcinoma of the colon with secondary carcinoma of liver and lungs.

Necropsy by Dr. K. M. Lynch. Body of a negro man about sixty years of age, of fair development and nutrition. Some jaundice of eyes and subcutaneous tissues.

Chest: The lungs have very few adhesions to the parietal pleura, and each pleural cavity contains about 25 cubic centimeters of fluid having a slightly bloody tinge. The lungs are generally crepitant except for numerous, varying-sized, white, firm nodules scattered throughout both lungs, some being just beneath the pleura.

Heart: Pericardial sac normal. Heart of about normal size, somewhat pale in color. Valves and valve orifices normal. Intima and endocardium jaundiced.

Abdomen: There is a very small amount of bloody fluid free in the peritoneal cavity. The mesenteric veins appear dilated and engorged, there being dilated veins on the inner surface of both recti muscles. No dilated veins on surface of abdomen noted.

Liver: Greatly enlarged and very rough, due to large lobulations and tumor masses of a white friable tissue, together with small nodules of hob-nail size of liver tissue. The tumor masses are of varying size and generally scattered throughout the liver; they show some central umbilication. Gall-bladder is thick, contains no stones, and bile flows into duodenum on pressure.

Pancreas: Firm and shows lobulations rather prominently; no tumor.

Spleen: Weighs 275 gms., firm, and somewhat fibrous.

Kidneys: About normal size, deformed in shape by pressure from the liver, causing them to be flattened; otherwise they show nothing of importance grossly.

Stomach and Intestines: The transverse colon and the hepatic flexure are very firmly adherent to the liver, being separated with difficulty; this appears to be due simply to adhesions, there being no infiltration of the tumor into the intestine. The mucosa of the intestine shows scattered areas which are quite hemorrhagic and apparently due to the portal congestion. No tumor of the intestines.

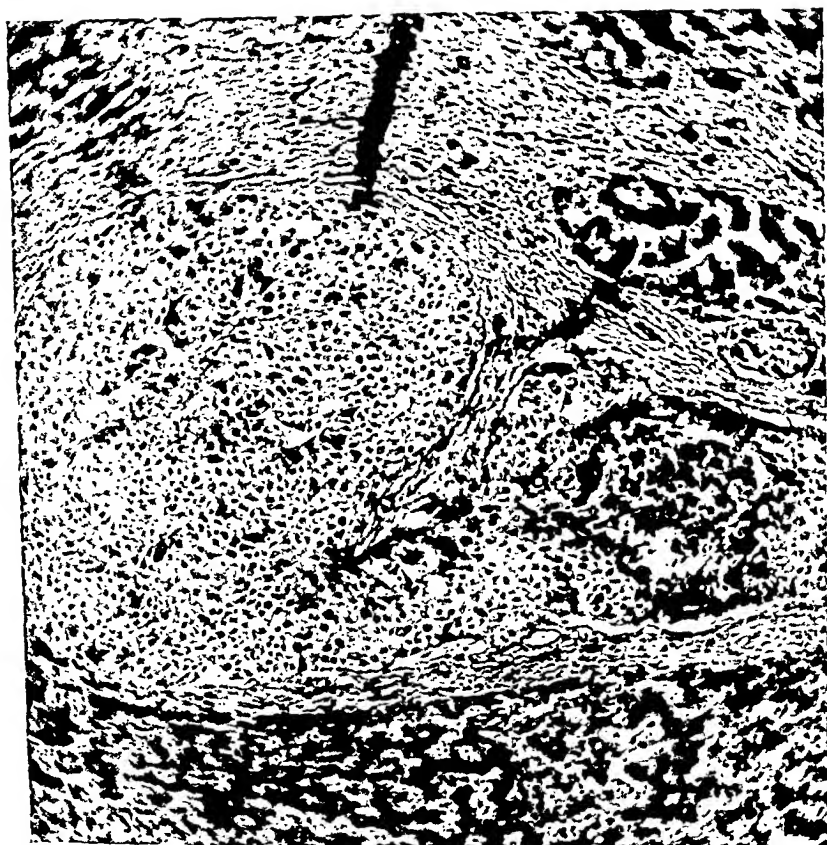
Prostate: Small, firm, tough.

Thyroid: Weighs 16 gms.

Microscopic Examination.—*Liver:* There are multiple new growths of tissue, having a somewhat rounded form, composed of atypical liver cells and arranged to some extent in chords and columns. There is some infiltration of liver tissue and plugs growing into portal veins. There is a very definite and marked increase of fibrous tissue about the portal vessels and around the lobules, the new growth apparently seems to have its beginning in the portal spaces. Some of the bile-ducts are filled with bile; many bile sinuses in the lobules are filled, and the liver cells stained a yellowish-green color in many lobules. (Fig. 1.)

Lungs: There are numerous segregated nodules of varying size composed of atypical liver tissue, with plugs of these same cells found in vessels of different size. The lung substance is congested.

FIG. 1.



CASE I.—Portal cirrhosis associated with primary liver cell carcinoma.

FIG. 2.



CASE II.—Primary liver cell carcinoma associated with portal cirrhosis.
Left lobe.

FIG. 3.



CASE II.—Primary liver cell carcinoma associated with portal cirrhosis.
Right lobe.

Pancreas: Islands not very numerous, some quite small and some of the larger ones show moderate fibrosis. Rather general increase of fibrous tissue with compression of the glands, and mononucleosis. The gland is very much lobulated by fibrous tissue.

Intestine: There is a rather marked congestion of the vessels, and surface necrosis of the mucosa, a good part of which is postmortem.

Prostate: Fibrosis and lymphocytosis; compression of glands; some hemorrhage into a few of the glands.

Thyroid: Variation in size of acini and in the apparent consistency of their colloid content, in some it is a bluish purple, others very pale pink and granular, while in some it is of a uniform pink hyaline type. General increase of fibrous tissue, causing some atrophy in parts.

Kidneys: Granular degeneration of the convoluted tubular epithelium, yellowish brown and some apparently yellowish green pigmentation of collecting tubules. Otherwise the kidneys are apparently in good condition.

Spleen: Blood-vessels and sinuses engorged with blood; rather heavy general increase of the fibrous tissue.

Heart: Muscle fibers not unusually large; their cytoplasm is fairly granular with loss of prominence of the cross striation. A few patches of fibrous tissue in the myocardium.

Pathologic diagnosis: Primary liver-cell carcinoma; metastases to lungs. Portal cirrhosis.

CASE II.—Clinical History.—P. M., a negro man forty-two years old, fireman, entered the Roper Hospital January 26, 1928, complaining of swelling of abdomen.

Family History.—Unimportant.

Previous History.—Measles in childhood; a sore on the prepuce and gonorrhea seventeen years ago; general anasarca fifteen years ago lasting about a month, and beginning in the feet. Has been a regular and a rather heavy drinker.

Present Illness.—About a month before entering the hospital he became very constipated, to overcome which he took salts frequently. The urine which had been very copious and frequent now became infrequent and difficult; this change was attributed to the salts. About the same time he began to suffer with pain in the abdomen, at first not severe but becoming more so recently. About a week after the onset of these symptoms he noticed a swelling of the abdomen which has gradually increased. His feet have been swelling a little. Slight dizziness and headache were associated with the constipation.

Physical Examination.—Quite emaciated with a greatly distended abdomen. Nothing abnormal was found in the chest. The blood-pressure was 95 systolic, 65 diastolic. The upper limit of liver dulness was in the fifth interspace but the lower border could not be palpated on account of the marked ascites. There was moderate edema of the lower extremities. The left epitrochlear and the inguinal glands were enlarged.

Laboratory Examination.—The urine had a specific gravity of 10.10 and contained some granular casts, but was otherwise normal.

The hemoglobin was 80 per cent., Dare. The leukocytes 9,280 with a normal differential cell count. Blood Wassermann and Kahn were negative. The direct Van den Bergh was negative, delayed direct 4 plus, indirect 4 plus. The blood

sugar was 110 milligrams, Urea nitrogen, 21.8 milligrams rising to 60.6 milligrams the day before he died. Creatinin was 1.3 milligrams.

The faeces were gray in color, contained 2 plus fat and no blood.

The ascitic fluid had a specific gravity of 10.06, and contained globulin gm. .8 per 100 cubic centimeters, albumin gm. .5 per 100 cubic centimeters, a few lymphocytes, an occasional polymorphonuclear leukocyte, and an occasional endotheliocyte. A growth of short chain streptococcus and Gram-negative coliform bacillus was obtained on culturing.

Clinical Diagnosis.—Portal cirrhosis with probable cancer.

Necropsy, partial, by Dr. K. M. Lynch. Negro man about fifty years of age. The body is somewhat emaciated and the abdomen distended with a large quantity of clear yellowish fluid.

The liver is large, weighing 1,937 grams, and very firm, retaining its shape. It is coarsely "hob-nailed" over the entire surface. On section it is composed of small lobules, generally varying in size from minute to about one-half inch in diameter surrounded by framework tissue. Through the left half of the organ these lobules are firm and pale. In the right portion the lobules are generally larger, some an inch or more in diameter, and are paler in color than those of the left, and are friable. The larger ones, particularly, are soft. The portal vein and its branches throughout the liver are practically completely occluded by a pale friable growth or substance. The gall-bladder walls are apparently somewhat thickened.

Microscopic Examination.—Liver: The left half of the organ shows a marked perilobular fibrosis, lymphocytosis, bile-duct increase, biliary accumulation, and extreme congestion. The lobules vary in size and the larger ones show large liver cells, especially at the periphery, some of which are bi-nucleated. Mixed with these ordinary liver-cell lobules are some in which the cells are very large, the nuclei of which are large, vesicular, hyperchromatic, and evidently multiplying. Sections from the right half show in addition to the cirrhosis almost entire replacement of ordinary liver tissue by lobules of the very large active cells and others in which the cells still resemble liver cells but are atypical in form, very large, and have nuclei extraordinarily active, large, vesicular, hyperchromatic, and dividing. The veins of this part are markedly distended with blood. It appears that growth of this atypical liver tissue is proceeding along the lumen of vessels in the perilobular stroma. Many of the atypical lobules show extensive necrosis. (Figs. 2 and 3.)

Pathologic Diagnosis.—Primary liver-cell carcinoma; portal cirrhosis.

These two cases of primary carcinoma of the liver both show essentially the same process. In each there is an old portal cirrhosis with a primary liver-cell carcinoma arising apparently from the hyperplastic cells of the lobules which have enlarged under the cirrhosis. There is extension through the portal venous system. In Case II, the primary focus appears to be in the right lobe and extensive infiltration has taken place through the venous channels with extensive occlusion of the portal system. The initial symptoms in both cases were obscure, and both ran a rapid course. In Case I the

large masses which were felt were sufficient warrant for the diagnosis of malignant disease, but there was nothing to indicate that it was a primary growth. The extensive pulmonary metastases gave no symptoms or signs upon which a diagnosis could be made. The diagnosis of this condition was made by the X-ray examination. Case II presented a typical picture of portal cirrhosis with a characteristic alcoholic history.

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THE DIAGNOSIS OF CHRONIC PANCREATIC DISEASE

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As long ago as 1875, Friedreich¹ taught that "fatty stools, mellituria, epigastric pains with the characteristics of celiac neuralgia, and a palpable tumor, lead among the symptoms most useful in diagnosis," of chronic pancreatic disease, and the presence of undigested, striated muscle fibers in the faeces "is worthy of every consideration and may, perhaps, be of diagnostic value."

Although Friedreich wrote this in an authoritative monograph in Ziemssen's System over fifty years ago, the importance of a careful study of the stools in the diagnosis of pancreatic disease is not yet common knowledge. Even today in few medical clinics are adequate microscopic and chemical studies made of the stools in cases of suspected pancreatic disease. There are surgeons who still write papers on the diagnosis of cancer of the pancreas without even mentioning the character of the stools.

FAT IN STOOLS

A fatty stool is a very light-colored stool. The presence of fat obscures the presence of bile, so that the stool may be clay-colored and yet contain hydrobilirubin in normal amount. It is often necessary to use Schmidt's corrosive sublimate test for bile before it can be decided whether the light color is due to a complete absence of bile resulting from an obstructive jaundice, or to the presence of a large amount of fat. The stools in obstructive jaundice contain much fat, as F. Müller² first showed. Sometimes a fat stool is of a glistening white color, but more often it is gray. The fat may occur in the form of oil. Stools containing liquid fat were noted in four out of twenty-nine cases of pancreatic disease with fatty stools collected by Fitz.³ Masses of fat looking like butter may separate from the stools, sometimes in an amount the size of a walnut. When fat is present, chiefly in the form of crystals, it may give the faeces the appearance of aluminum paint. At times, liquid fat is passed, which solidifies on cooling. Liquid fat and the solid masses of fat

looking like butter are passed with the stool but usually detached from it. In two cases, Tileston⁴ found small masses in the faeces resembling pus, but which were found on microscopic examination to consist entirely of neutral fat globules. Fat may rarely occur in small, white, crumbly masses. These consist of fats with high melting points. Tileston found them in one out of five cases. He noted the presence of macroscopic fat in five out of six cases of pancreatic disease that he studied. "For its detection it is only necessary that the stools be examined frequently while the patient is on a diet fairly rich in fat (preferably in the shape of butter, cream, eggs, or olive oil), and that the stools when formed should be cut across with a knife, as the fat is sometimes in the interior of the stool when there is none on the outside" (Tileston). Whether a patient with obstruction of the pancreatic ducts passes an oily stool or one containing fat that looks like butter doubtless depends upon the form of fat that is fed. The oily liquid fat in the stool is the liquid fat, such as olive oil, in the food, and the butter-like stool is formed from the butter the patient has eaten. This was shown by Rosenblum and Krakower working in my laboratory at the Tufts Medical School the past year. Studies were made on a dog in which no pancreatic juice entered the intestine, as was later verified by an autopsy. When even a small amount of olive oil was fed, about three gms. per kilo, the stools were found to contain liquid fat. They obtained the iodine number of the fecal fat and found it to be that of olive oil. When a fat with a lower iodine number was fed, such as butter, the iodine number of the fecal fat closely approached that of butter. In a normal dog, on the other hand, when olive oil or butter was added to the diet in the same amounts given to the dog without pancreatic juice, the iodine number of the fecal fat was unchanged, as Bloor has previously shown. The fat normally present in the stool does not originate in the fat of the food, but is secreted by the intestinal mucosa.

Fat in the faeces occurs as neutral fat, fatty acids, and soaps. Neutral fat appears as oil drops or as irregular flakes depending upon its melting point. In the stools of adults, neutral fat generally occurs in drop form. Frequently the drops are found coalesced into structures of irregular shape. They are often colored yellow. When heated, the flakes are converted into large drops. The addition of an alcoholic solution of sudan III to a preparation colors the

neutral fat red. A concentrated solution of Nile-blue sulphate gives it a rose-red hue (Lohrisch⁵). Fatty acids and soaps are colored blue by Nile-blue sulphate.

Fatty acids occur as various types of needle crystals, drops and flakes. With diluted Ziehl's solution of carbolfuchsin, they stain intensely while neutral fat remains uncolored.

The soaps have the form of flakes or crystals. The soap flakes are less refractive, have a firmer consistence, and more angular polygonal contours than the flakes made up of neutral fat and fatty acids. The flakes are often colored yellow with hydrobilirubin forming the yellow calcium salts described by Nothnagel.⁶ Soap crystals are usually shorter and less pointed and less curved than fatty-acid crystals. On heating a preparation, neutral fat and fatty-acid crystals are converted into oil drops but the soap crystals remain unchanged. Almost all fatty stools contain neutral fat, fatty acids and soaps in varying proportion. A simple way to determine roughly the amount of fat present in a stool is by heating on a microscopic slide over a Bunsen flame a few drops of a fecal suspension to which a drop of 30 per cent. acetic acid has been added. A cover slip should be placed over the preparation before heating. If much fat is present, nearly the entire specimen appears to be converted into fat drops. On cooling, if the drops be composed of fatty acids, crystals form in them, but if they are made up of neutral fat, the drops remain unchanged.

Bulkiness of the stools is an important diagnostic feature in obstruction of the pancreatic ducts. In no other disease condition does one see such massive dejections. They are usually formed, rarely if ever watery. In obstructive jaundice, grayish-white glistening stools resembling somewhat those in pancreatic disease, may be seen, but they are not bulky. Not only are the stools bulky, but the weight of the faeces excreted in a day is greater in complete obstruction of the pancreatic ducts than in any other morbid state. The voluminous stool is probably the most important single subjective sign of pancreatic disease. According to v. Noorden,⁷ the weight of the fresh faeces sometimes may be as much as a kilogram. One of my dogs, Zep, that lived nearly three years after the pancreas was separated from the duodenum, passed faeces in a four-days' absorption experiment that had a weight when dried of 2,703.4

gms. The dried weight is rarely as much as 25 per cent. of the weight of the stools when passed, but assuming in this experiment that it represented 25 per cent. of the original weight, then the fresh stools weighed 10.8 kilos. If so, the average daily weight of the excreta was 2.7 kilos, or more than five pounds! The dog weighed 6.5 kilos at the beginning of the experiment. During the four days of the test, the weight of the fresh stools passed exceeded the weight of the dog.

In studying the digestion and absorption of food in pancreatic and intestinal disease, it is helpful to use the standard diet devised by Adolf Schmidt. It is easily prepared and it is palatable. In its composition are enough meat, fat, and starch to bring to light faulty digestion of these substances if there is a functional impairment of pancreas or intestines. As only a few articles of food enter into the composition of the diet, the microscopic examination of the faeces is simplified. Adolf Schmidt made careful analyses of the stools of patients with different diseases who were on this diet. They are given in the classical work he wrote with Strasburger⁸ on "Die Faeces des Menschen." That the results by different investigators can be compared is the chief advantage of his diet over others that might be used. The fourth and last edition appeared in 1915, but no work since published has equalled it in value. Unfortunately, it has never been translated into English.

The details of the diet I have used for many years are given in the English translation by Doctor Aaron of Detroit of Schmidt's Test Diet in Intestinal Diseases.⁹ It consists of "1.5 liters milk, 100 gms. zwieback, 2 eggs, 50 gms. butter, 125 gms. beef, 190 gms. potatoes, and gruel of 80 gms. oatmeal. It contains about 120 gms. protein, 111 gms. fat, 191 gms. carbohydrates, or a total of 2,234 calories.

"In the morning: 0.5 liters milk (or, if milk does not agree, 0.5 liter cocoa prepared from 20 gms. cocoa powder, 10 gms. sugar, 400 gms. water and 100 gms. milk) and 50 gms. zwieback.

"In the forenoon: 0.5 liter oatmeal gruel (made from 40 gms. oatmeal, 10 gms. butter, 200 cubic centimeters milk, 300 centimeters water, 1 egg, strained).

"At noon: 125 gms. chopped beef (raw weight), broiled rare with 20 gms. butter, so that the interior will still remain raw, and 250

gms. potato broth (made of 190 gms. mashed potatoes, 100 cubic centimeters milk, and 10 gms. butter.)

"In the afternoon: As in the morning.

"In the evening: As in the forenoon."

This diet should be continued for three days.

With the first meal, to mark off the stools give 1 or 2 gms. charcoal, or 0.5 gm. carmine. Begin to save the faeces when the coloring matter first appears. The morning after the diet is finished, again give a dose of carmine or charcoal. Continue to save stools until coloring matter appears. Discard the first stool that is colored.

In the following table are given the average weights of the dried stools obtained from the Schmidt diet during a three-day period. It is taken from the last edition of "Die Faeces des Menschen." The analyses were made by Schmidt, except in the case of obstruction of the bile and pancreatic ducts which I reported, but which Schmidt included in his table.

TABLE I

	Weight of Dried Stools in Three-day Period Gms.
(1) Normal, average in six cases.....	54.3
(2) Obstructive jaundice, four cases.....	175.6
(3) Hypochylia pancreatica, two cases.....	132
(4) Obstruction of bile and pancreatic ducts, one case.....	419
(5) Fermentative dyspepsia, five cases.....	127.4
(6) Gastrogenous diarrhea with achylia gastrica.....	98.9
(7) Severe enteritis, one case.....	186.5

It will be seen from this table that the weight of the faeces in the single case of pancreatic and biliary obstruction was over twice the average figures in any other condition. The nearest approach to it was one case of obstruction of the bile-ducts in which the dried stools weighed 215.4 gms. In a second metabolism experiment on the case of mine included by Schmidt in his table, the weight of the dried stools was 355 gms. In a patient with obstruction of the pancreatic ducts without icterus studied by Morrison and me at the Massachusetts General Hospital, the dried faeces collected during the three-day period on the Schmidt diet weighed 438 gms. This,

I think, is the highest ever reported. The rarity of cases with complete exclusion of the pancreatic juice from the intestine is shown by the fact that Schmidt never had the opportunity to study one in his clinic and the only ones he found in the literature in which

TABLE II

No.	Disease	Name	Percentage of Fat in Dried Stools	Amount of Fat Excreted in Three Days	Percentage of Fat in Food Unabsorbed	What Percentage of the Fat Is Split?
1	Normal.....	L	21.45	12.93	5.17	60.29
2	Normal.....	W	21.93	13.6	5.43	64.31
3	Normal.....	K	26.61	14.8	5.91	56.89
	Average.....	23.24	13.78	5.50	60.5
4	Gastrogenous diarrhea.....	Ja	12.55	14.08
5	Gastrogenous diarrhea.....	Lic	42.95	19.95
	Average.....	27.70	17.01
6	Fermentative diarrhea.....	Br.	19.45	19.29
7	Fermentative diarrhea.....	B.	21.18	21.9	8.75	69.90
8	Fermentative diarrhea.....	D	22.19	35.48	14.18	90.70
	Average.....	20.94	25.56	11.47	80.3
9	Biliary obstruction.....	V	48.48	57.13	22.79	67.06
10	Biliary obstruction.....	D	43.87	69.31	27.70	46.45
11	Biliary obstruction.....	G	53.59	68.06	27.20	85.00
	Average.....	48.65	64.83	25.89	66.84
12	Complete occlusion of the pancreatic ducts without icterus.....	Mc	61.30	268.5	49.10	43.4
13	Disturbance of absorption from intestine.....	Kal	30.48	32.92	13.15	75.84
14	Disturbance of absorption from intestine.....	Ker	34.15	52.93	21.11	47.38
	Average.....	32.32	42.92	17.13	61.61
15	Chronic constipation.....	Gr.	23.6	8.74
16	Chronic constipation.....	M	25.9	7.98
17	Chronic constipation.....	GW	21.7	8.02
18	Chronic constipation.....	JN	23.6	7.93
	Average.....	23.8	8.17

the patients had been studied with the aid of his diet were those I reported.

Not only are the stools in pancreatic obstruction heavier than in other conditions, but the amount of fat excreted is greater. This is clearly shown in the preceding table from Schmidt's book. The only case of pancreatic duct obstruction he gives is the one I studied with Morrison.¹⁰ All the patients were on the Schmidt diet. It will be noted that the percentage of fat in the faeces as well as the amount of fat excreted is more than in any other disease. Note that our patient's stools contained 268.5 gms. of fat while the largest amount observed by Schmidt on the same diet was 69 gms. This was in a case of obstructive jaundice.

The presence of an increased percentage of neutral fat in the stool is sometimes found in pancreatic obstruction. In a case of v. Noorden it formed 91.6 per cent. of the total fat. This table, for example, shows that the largest per cent. of neutral fat was found in our case of occlusion of the pancreatic ducts. In four out of seven cases of chronic pancreatic disease I observed some increase in the neutral fat. A low percentage of soaps is often found and may be of aid in diagnosis. In three of my seven cases, it was less than 20 per cent. Deficiency of the alkali ordinarily furnished by the pancreatic juice seems to be the cause of the small amount of soaps. In dogs, the fat in the absence of pancreatic juice is always well split and the percentage of soaps is not diminished. The fat in food removed after death from the jejunum and ileum of one of our dogs contained a large percentage—40-50—of split fat, 41.5 per cent. in the jejunum and 46.4 per cent. in the lower part of the ileum.

I have had a number of cases of non-pancreatic disease with a larger amount of fat in the faeces on the Schmidt diet than any observed by Schmidt himself. In a case of obstructive jaundice I studied with McClure, the percentage of fat was 73.3 and the amount of fat excreted in the three-day period was 96 gms. The highest percentage of fat I have ever found in the dried faeces when using the Schmidt diet was 86.2 per cent. This was not a case of pancreatic or biliary obstruction, but of tropical sprue. In another case of sprue on this diet the percentage of fat was 49.53.

For the past twenty-five years I have studied whenever possible all cases with an excess of fat in the stools. The condition is not

very common. I suppose obstructive jaundice is the most frequent cause of fatty stools. In most clinics it is unusual to have an opportunity to see them in any other condition. In distinguishing between biliary obstruction and pancreatic obstruction the weight of the dried stool is usually a far safer guide than the percentage of fat present. In the case of obstructive jaundice just mentioned that McClure and I studied, the total weight of the dried faeces was only 131 gms. It will be noted that is less than the average weight in obstructive jaundice given in Table I, which is 175.6 gms.

Sprue is characterized by stools that are very rich in fat. This is a point to which most writers on that disease do not attach sufficient importance. It is a great aid in distinguishing it from other forms of diarrhea and from pernicious anemia. In two cases I was greatly puzzled in attempting to decide whether I was dealing with cancer of the pancreas or sprue. In the case with 86.2 per cent. of fat in the stools, McClure and I found the total weight of the dried stools to be only 149 gms. This low weight was important in diagnosis as the case proved to be sprue. A complete recovery followed.

Rapid progress of food through the intestine may give rise to a fatty stool. I had one such case. After the patient passed this fatty stool, I sent her at once to the hospital and examined the subsequent stools carefully but they did not contain an excess of fat on the Schmidt diet. Carmine appeared in the faeces, two and a half hours after it was taken by mouth!

Years ago a patient brought me a fatty stool of small size. She had much epigastric pain, brought on by taking food. I hazarded the diagnosis of pancreatic calculus. It proved to be cholelithiasis. The gall-bladder was filled with small gall-stones. With its removal the pain ceased. The fatty stool was apparently due to starvation. v. Müller found that the starvation stools of two professional fasters which he examined contained an excess of fat. My patient had eaten practically nothing for a week or more prior to passing the stool.

NITROGEN IN THE STOOLS

Undigested muscle fibers have been found in large numbers in the stools of patients who had complete obstruction of the pancreatic ducts. It is a constant finding in dogs when the pancreas is entirely

separated from the duodenum and a diet rich in meat is given, as I and my co-workers have observed. To this condition the name *creatorrhea* is applied. Under the microscope the muscle fibers have sharp edges and the striations are well preserved. Occasionally a number of fibers are united together, forming a small mass of brownish color visible to the naked eye. Poor digestion of muscle fibers and of other food rich in protein is the chief cause of an increase of the nitrogen content of the faeces in pancreatic disease.

The employment of the Schmidt diet permits a comparison of the nitrogen excretion in various diseases and shows that it is greatest in obstruction of the pancreatic ducts. The following table is based on one given by Adolf Schmidt in "*Die Faeces des Menschen*."

The Schmidt diet was used in all cases.

TABLE III

	Amount of Nitrogen Excreted Daily Gms.	Percentage of Nitrogen in Faeces
(a) Normal.....	.99	5
(b) Occlusion of common bile-duct.....	2.05	4.14
(c) Constipation.....	0.52	4.57
(d) Diarrhea.....	1.57	6.74
(e) Nervous diarrhea.....	1.07	4.5
(f) Ulcerative colitis.....	1.72	5.6
(g) Sprue.....	2.71	6.03
(h) Sprue.....	1.59	3.02
(i) Occlusion of common bile-duct.....	1.11	2.55
(j) Fatty diarrhea not due to pancreatic disease.....	2.15	4.56
(k) Complete occlusion of pancreatic ducts...	8.49	5.82

The analyses in the first four cases were made by Adolf Schmidt, those in the last seven by my associates and myself. It will be noted that next to pancreatic obstruction the largest amount was in a case of sprue. The percentage of nitrogen has little or no significance. It was highest in a case of diarrhea but the amount of nitrogen excreted daily was small.

CARBOHYDRATES IN THE STOOLS

Few studies of the digestion and absorption of starch in pancreatic disease have been made. In fact, there are few published

analyses showing the amount of starch in the faeces in any disease. In jaundice the utilization of starch is equal to that in health. Schmidt found the greatest disturbance in catarrh of the small intestine. In four of his cases of intestinal fermentative dyspepsia the percentage of starch recorded as sugar in the dried stools ranged from 3.33 to 7.43 and the amount in a three-day test from 4.09 gms. to 5.93 gms. In a case of severe intestinal catarrh, the percentage was 9.69 and the total amount of starch in a four-day experiment was 27.37 gms.

It was claimed by Friedrich Müller and some other of the older writers that the digestion of carbohydrates was not impaired in disturbances of pancreatic secretion. Rosenberg,¹¹ many years ago, found in animal experiments some defect in the utilization of carbohydrates. Starch granules are readily recognized in the faeces by their dark blue color when a drop of Lugol's solution is added to the preparation.

In ten or more dogs we have excluded all pancreatic juice from the intestine by separating the pancreas from the duodenum and interposing omentum between the two structures. When no pancreatic secretion enters the duodenum, the animals lose weight even when fed large amounts of food. The stools are bulky and increased in number and weight. They are found on microscopic examination to consist largely of undigested muscle fibers and fat in the form of oil drops. In January, 1923, I had under observation a dog in which the attempt to shut out all the pancreatic juice from the intestine had evidently failed. The dog's diet contained a large amount of meat, butter, and cracker meal. The stools were small and few. The muscle fibers of the meat fed were digested and there was no apparent excess of fat. On adding Lugol's solution to a microscopic preparation of the stool, a large number of blue-stained starch granules were seen. They were, in fact, so numerous that the blue color was visible to the naked eye. The dog did not lose weight. This observation indicated that we had produced a condition in which sufficient pancreatic juice was entering the intestine to digest the muscle fibers and fat but not all of the starch. Writers have described clinically cases that are termed *hypochylia pancreatica*. Here we had a *hypochylia pancreatica* in a dog.

The method in use at the time for determining the carbohydrates

in the stool was complicated and time-consuming. As a result, few studies of the utilization of starch in diet had been made. Dr. Hjort, then working with me, devised a new and simple method for the quantitative analysis of starches in stools. It consists of obtaining a clear fluid from a hydrolyzed fecal suspension by the use of Lloyd's reagent and of determining the amount of sugar by Folin's method for blood sugar. Later Hershenson showed the reliability of the method and we have used it with some modifications in our laboratory in a number of cases of pancreatic insufficiency and intestinal diseases.

Hjort made a study of the carbohydrate absorption in the dog just mentioned which had a lessened secretion of pancreatic juice. Before the operation in a three-day experiment, the dog, weighing 10.1 kilograms, ate daily 400 gms. ground meat, 200 gms. cracker meal, and 135 gms. butter. The total weight of the dried stools was only 20 gms. They contained 1.08 per cent. of starch estimated as sugar, amounting to 0.216 gms. The percentage of sugar utilized was 99.95 per cent.

A week after the operation another three-day absorption test was made. 320 gms. ground meat, 160 gms. cracker meal, and 108 gms. butter were fed each day. The dried stools weighed 78 gms. The sugar was 14.23 per cent.; the amount was 11.1 gms. In comparing the results of these two experiments, it will be seen that after the pancreatic juice had been partly excluded from the intestine, the amount of carbohydrates in the stools was increased fifty times. There was some disturbance also in the absorption of nitrogen, revealed by the chemical analysis, only 71.8 per cent. being utilized, instead of the normal 90 per cent. or more. The fat absorption was 98.45 per cent., which is within normal limits.

DEFICIENT ABSORPTION OF NITROGEN, FATS AND STARCH IN PANCREATIC OBSTRUCTION

Falcon-Lesses and Hershenson found that by giving a carefully regulated diet to a dog without pancreatic juice there was fairly good absorption of nitrogen, fat, and starch, so that gain in weight occurred. In my previous work, when dogs deprived of pancreatic secretion were allowed to eat freely, they lost about 50 per cent. of both the nitrogen and fat of the food and invariably lost weight

unless fresh pancreas was fed. In fact, some dogs died of inanition, although they ate large amounts of food. The large percentage of starch lost in the stools in the following experiment was the result of feeding uncooked whole wheat. The absorption of food was studied in two dogs, each weighing about 11 kilograms. The daily diet for each was 125 gms. ground meat, 100 gms. whole wheat, 50 gms. dried milk powder, and 50 gms. lard.

TABLE IV
Four-day Period

	Weight Dried Stools Gms.	Nitrogen Absorbed Per Cent.	Fats Absorbed Per Cent.	Starch Absorbed Per Cent.	Unde- termined Residue Gms.
Normal dog.....	73	92.2	98.2	92.1	37.3
Dog with pancreatic juice excluded from intestine.....	158	85.3	93.6	73.9	52.49

At the autopsy no connection existed between the atrophied pancreas, which was reduced to a narrow cord, and the duodenum. No analysis has been previously published showing such good utilization of food when no pancreatic juice was entering the intestine.

These results were confirmed the past year by Rosenblum and Krakower working in the Chemical Laboratory at Tufts Medical School. They did absorption studies on a dog, before and after the exclusion of pancreatic secretion from the intestine. It will be seen that the substitution of cracker meal for the whole wheat led to a better absorption of carbohydrates. The diet employed was 50 gms.

TABLE V
Three-day Period

	Weight Dried Stools Gms.	Nitrogen Absorbed Per Cent.	Fats Absorbed Per Cent.	Starch Absorbed Per Cent.
Normal dog: Dutchy.....	43	90.8	94.9	98.9
Same dog after excluding pancreatic juice. Experiment II.....	195	46.8	63.8	79.3

in the stool was complicated and time-consuming. As a result, few studies of the utilization of starch in diet had been made. Dr. Hjort, then working with me, devised a new and simple method for the quantitative analysis of starches in stools. It consists of obtaining a clear fluid from a hydrolyzed fecal suspension by the use of Lloyd's reagent and of determining the amount of sugar by Folin's method for blood sugar. Later Hershenson showed the reliability of the method and we have used it with some modifications in our laboratory in a number of cases of pancreatic insufficiency and intestinal diseases.

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TABLE VI
Three-day Period

	Weight Dried Faeces Gms.	Nitrogen Absorbed Per Cent.	Fats Absorbed Per Cent.	Starch Absorbed Per Cent.
Depancreatized dog	105	56.2	95.24	98.5

have resulted. In this experiment the absorption of all these food-stuffs was actually greater in this dog deprived of all pancreatic tissue, than in Experiment II, on the dog Dutchy, in which the pancreatic juice was simply excluded from the intestine.

CONCLUSIONS

Our studies to date show that the fat and starch digestion and absorption in dogs can be kept within normal limits without the aid of pancreatic juice. Nitrogen absorption is always somewhat deficient. By feeding a large amount of either protein, fat or starch, a gross loss in the stool will be obtained when the pancreatic juice is absent. When pancreatic secretion is present, but small in amount, starch, if fed in large quantity, may be recognized in the faeces by staining blue with iodine even when meat fibers and fat are not present in sufficient amount in the stools to indicate on microscopic examination the presence of pancreatic insufficiency.

Dogs without pancreatic secretion entering the intestine have always been found by us to lose weight when allowed to eat large amounts of food. They died of inanition even when they filled their stomachs daily with nutritious food.

The results of this work on animals suggest new methods that may be useful in the diagnosis and treatment of patients with chronic pancreatic disease.

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DISCUSSION

The case appears to be a unique one in medical literature and there is little to say in the way of discussion beyond recording the facts. It is evident, however, that the reasons for incriminating the spleen which have been invoked in these cases do not hold in the present instance and the reason for the platelet deficiency remains obscure. Intensive morphologic blood studies at no time showed changes other than the thrombopenia and such alterations as might be expected secondarily to the prolonged and repeated blood loss. The possibility of an atypical leukemia was considered but no support for such a diagnosis was forthcoming. The leukocyte count varied from normal values up to 20,000 and at times a few myelocytes and an occasional myeloblast were present. However, during the terminal stages the leukocyte count was quite normal, as for example on March 6:

White blood-cells, 7,000
Polymorphonuclears, 64 per cent.
Lymphocytes, 34 per cent.
Mononuclears, 2 per cent.

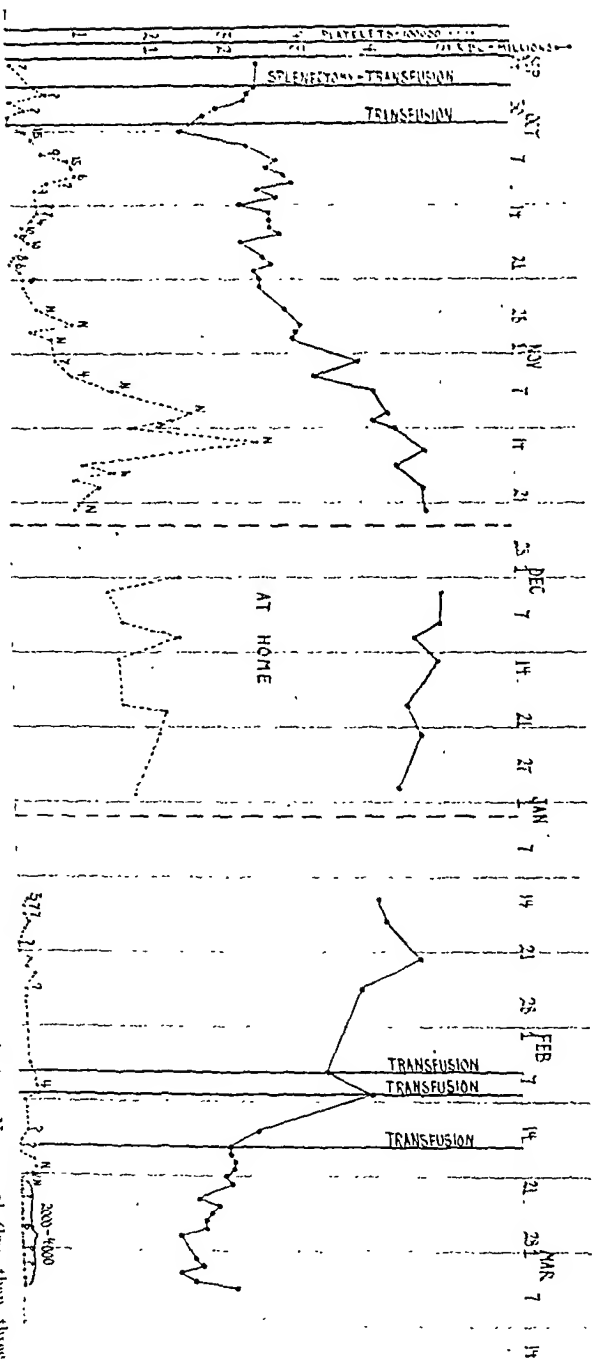
Nor did the histologic picture of the spleen (see below) suggest leukemia.

A point of special interest is the relation of the platelet count to the bleeding time. The latter is indicated in figures above the platelet curve in Chart I. No absolute relationship is made out; indeed, at times the bleeding time was greatly prolonged with platelet counts of nearly 100,000 while at other times it was almost normal as on February 27, with platelets of only 3,000. Nor was there any absolute relationship between clinical bleeding and purpura. Slight rises in platelet count were noted several times following transfusion. They did not seem explainable by introduction of foreign platelets alone. The only significant rise in platelets occurred during November, apparently as a spontaneous remission.

The hemoglobin values varied closely with the red-cell count and therefore have not been charted.

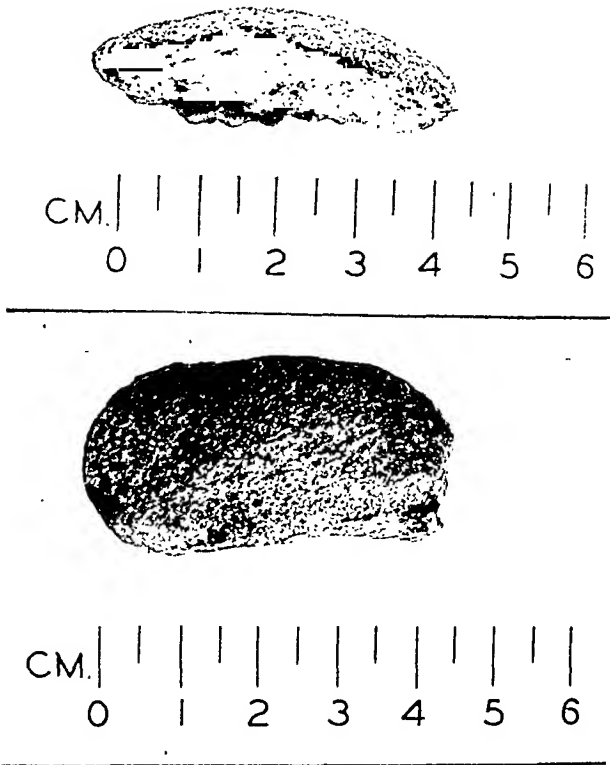
Examination of the excised spleen was as follows: the specimen measured 4.7 by 2.5 by 1.2 centimeters and weighed eight gms. The capsule was finely granular, wrinkled and pale. "Sections show a thickening of the trabeculae which occupy the greater part

CHART I.



Course of blood counts in patient J. MacG. The numbers above the platelets counts indicate the bleeding time in minutes. N. = normal (less than three minutes); \circ = indefinitely prolonged.

FIG. 1.



Photograph of spleen removed at operation.

of the field, separated by small amounts of pulp tissue, the venules of which are surrounded by a heavy proliferation of loose connective tissue. The pulp cells are few in number and the Malpighian bodies are somewhat atrophied. The small arteries show a marked fibrous thickening and hyaline degeneration. Scattered here and there are small numbers of fibroblastic cells filled with a brownish yellow granular pigment." Doctor Wyckoff studied smears from the spleen and noted that "the cells usually found in the splenic pulp are seen—polymorphonuclear neutrophiles, a few eosinophiles and very many erythrocytes. Normoblasts and a few megaloblasts are present. There are large numbers of platelets—more than are usually seen in blood smears. Some of the platelets are very large, varying in size up to 5.5 micra. Phagocytic cells are not easily found. A few elongated fusiform mononucleated cells containing granules are seen."

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Quarterly Cumulative Index Medicus, vol. 9, No. 1, 1931.

Clinical Papers on Diseases of Brain

DUPUYTREN'S CONTRACTURE AND THE UNCONSCIOUS

A Preliminary Statement of a Problem¹

By SMITH ELY JELLIFFE, M.D., Ph.D.

New York

INTRODUCTION

For some time past the thought has been forcing itself into consciousness that I might like to say something about the human hand, something perhaps new, or novel, or different. But the longer I reflected and as more and more material, half-known, half-conjectural, came to the surface, the more prodigious seemed the affair. As through a glass darkly I loosely shuffled the scattered material dealing with the gradual ascending transcendence of the hands' activities throughout the primate series in its anatomic, physiologic, and psychologic advance. I knew where to start with the outlines of a monographic survey of the whole situation, but the longer I shuffled, the greater became my awareness of the futility of such an effort.

Then it seemed maybe one could limit the field and discuss just hands—the broad ones, the long ones, the fat ones, the thin ones; the leptosome hand, the pyknic hand, the thyroid hand, the pituitary hand, the eunuch hand; the artistic, the working, or whatever kind of hand, so intriguing to the pseudoscientific interests of the palm-reader or other exploiter of human credulity.

Even here a monograph awaited the serious worker. So, throwing all such pretentious dreams to the winds, I would pick up a curious specimen and offer some possibly bizarre speculations concerning a chance finding turned up in the course of my daily work.

As many a stroll over the countryside has been temporarily

¹ This paper, in sketch, was prepared for a discussion at the Vidonian Club of Neuropsychiatrists, January, 1931.

halted by the sight of a unique botanic specimen which, on being brought home to the study table, has offered many hours of pleasant scrutiny and speculation, so, in the present instance, while delving intensively into the unconscious life of a sorely tried individual seeking relief from an agony of apprehension and of bodily distress, a unique type of "hand specimen" here would claim some moments of reflection and fragmentary recording.

It is far from my intention to offer a monograph on Dupuytren's contracture. At the present time it is quite evident that the process that leads to the classic picture is far from being a unitary one. There are undoubtedly more than one series of factors involved in different cases, yet certain underlying possibilities offer an excellent opportunity for conjecture and research.

EARLY DESCRIPTIONS

It is not without a certain historic interest that the first physician who emerged from the scholastic morass of medievalism, so far as psychiatry was concerned—Felix Platter (1641)—is thought to have recorded the first instance of the kind of hand in question, and further, it may be stated that the present year is the one hundredth anniversary of the definite naming of the condition of which I would speak. In 1831, Baron Dupuytren clearly described and more accurately outlined the essential integrity of the type of deformed hand which has since borne his name.

As with many new discoveries, controversy was rife. Dupuytren had to meet the orthodox giants of his day—Malgaigne and Velpeau—who tried to maintain that here was no new find. It was, they maintained, only an expression of a contraction of the tendons of the voluntary deep and superficial flexors. Dupuytren's masterly dissections of the palmar aponeurosis which showed the complete uninvolved of the voluntary muscular attachments were sniffed at by the orthodox, until Langenbeck threw the weight of his authority on Dupuytren's side.

Dupuytren's careful dissections disposed of both deep and superficial tendon involvement. His early account is worth noting briefly.¹ In his "*Lecons orales de Clinique Chirurgicale*" it is stated

¹ See ADAMS, W.: "Contractions of the Fingers," pp. 5-6, London, 1892.

(1831), "A man who for some time had been under the observation of M. Dupuytren, and was the subject of this deformity, died, and M. Dupuytren succeeded in gaining possession of the arm and hand. A careful drawing was made of the parts before the dissection. The whole of the skin was removed from the palm of the hand, as well as from the palmar surface of the fingers. The result was the complete disappearance from it of the folds into which it had been gathered. This opening out showed that its arrangement during the disease was communicated to it; but in what way or by what means was not evident. Continuing the dissection, the professor exposed the palmar aponeurosis, and was surprised to find it stretched, retracted, and shortened. From its inferior part were given off bands which passed to the sides of the affected finger. On making movements of extension in the affected fingers, M. Dupuytren observed that the aponeurosis underwent a kind of stretching and crackling. This threw light on the subject. It seemed clear that the aponeurosis was somehow connected with the deformity produced by the disease. The affected point remained to be discovered. The prolongations to the sides of the fingers were then divided; the contraction disappeared at once, and the fingers assumed their normal condition of one-third flexion. The smallest force was now sufficient to bring them into a state of complete extension. The tendons were not implicated in any way, and their sheaths had not been opened. All that had been done was the removal of the skin, and the division of the bands of aponeurosis going to the bases of the phalanges.

"In order to remove all doubt and objections, M. Dupuytren dissected out the tendons. They retained their natural volume and mobility, as well as the smoothness of their surfaces. Continuing the examination, it was found that the articulations were in their natural condition, the bones not enlarged, roughened, or presenting in any way, either internally or externally, the smallest degree of change. No alteration was observed in the apposition of the articular surfaces, nor in their external ligaments; no ankylosis. Nor had the synovial sheaths, or the cartilages, or the synovial membranes undergone the slightest change. The conclusion naturally arrived at from these conditions was that the starting point of the disease was the excessive tension of the palmar aponeurosis. As regards the cause of the palmar lesion, it was considered to result

from injury to the aponeurosis caused by the too violent, or too prolonged action of some hard body held in the palm of the hand."

Since Dupuytren made this important contribution to our knowledge of this affection, in the year 1831, it has sometimes been spoken of as Dupuytren's finger-contracture, a title as useful as it is also a just compliment to the great surgeon, distinguishing it from all other forms of finger-contracture.

Since 1831 there has been almost no question that the process involved the palmar aponeurosis, in a fibrosing, proliferative activity involving the connective-tissue elements with secondary contractures. There are certain analogies to a fibrosarcomatous process which led many dermatologists before and some few since to deal with the disorder among the dermatoses. Alibert and Jules Guerin were among these. This general point of view has been entirely abandoned.

Practically all modern discussions of the problem speak of the situation as *inscrutable from the standpoint of meaning*.

To present the present-day position a short description of Dupuytren's contracture is taken from the account written by Dr. Sterling Bunnell for Dean Lewis' *Loose Leaf Surgery*, vol. 3, p. 118, 1928. This is chosen from the mass of literature as to the point and also for reasons to be noted later.

"This condition is a progressive flexion contracture of one or more fingers, due to a fibrous hyperplasia and contracture of the palmar fascia and its digital prolongations. It is usually bilateral, one hand being affected earlier and to a greater extent than the other. Though it comes more frequently at the rheumatic age in men past middle life, it is occasionally seen in youth. Rarely it subsides spontaneously but as a rule is progressive and permanent. Heredity is a factor. One in four have some family history of it and Krogus reports its occurrence in fifteen descendants of one family. It is frequently associated with gout and osteo-arthritis, and foci of infection and metabolic influences are probably more etiologic factors than is trauma. Trauma no doubt aggravates the condition as tension and friction always increase fibrosis, but when we consider that it is no more frequent in manual than in non-manual workers and that the right hand is not affected much more than the left, it cannot be assumed that trauma is a prominent cause of the condition.

That some generalized condition is responsible is suggested by a case seen by the author in which bilateral Dupuytren's contracture and contracture of the fascial septal band between the corpus cavernosum and the corpus spongiosum of the penis occurred simultaneously.¹

The contracture generally starts in the ring finger, then the little, middle, index and sometimes the thumb, in order of frequency. The contracting bands of palmar fascia stand out in the hand and radiate from the insertion of the *palmaris longus* tendon in the annular ligament. The bands can be followed down the fingers in lateral prolongations spanning the middle-finger joints to their attachment to the sides of the middle phalanx.

My patient, some of whose symptoms may be narrated later, had suffered since young boyhood with a gradually progressive Dupuytren's contracture in both hands for nearly forty years. It began in the right hand and then involved the other hand some years later, although it was never as intense in the left hand until recently.

He was about twelve to fourteen when he noted the difficulty first in the right hand and in the ring and little fingers of that hand—some time later, at least seventeen years, the left hand was involved. He is certain that his father had some of the same difficulty and also that his father's mother was likewise involved.

Nothing came out about the possible implication of the feet until analyzing a dream, when it developed that one foot was also involved. He has no involvement of the penis.

Seventeen years previously a local surgeon operated on the right hand with much comfort, if not complete relief, for fifteen years, but in the past two to three years another operation was necessary and the left hand was also operated on to facilitate his game of golf.

Among the numerous contributions looking towards a deeper understanding of Dupuytren's contracture which might be utilized to throw light on not only the central psychologic conception here suggested but also illustrative of a principle that would aid in the understanding of the at times very striking heredity factor are papers by Krogius and Kajava which are of special significance. The former deals specifically with the problem of Dupuytren's con-

¹ Italics ours.

tracture, the latter only with certain phyletic anatomic facts of the hand musculature.

Krogius, stimulated by the discussion of Kajava, believed that a more thorough central hypothesis was necessary than the traumatic (Dupuytren), gout, rheumatism, arteriosclerosis, tuberculosis, syphilis, alcoholic, central or peripheral nervous lesions, *etc.*, all of which would herewith be discussed if a complete account were contemplated.

He was struck by the symmetrical involvement in both hands in most cases and also by the beginning history, either of fourth- and fifth-finger implication or in some isolated cases of the fifth finger alone starting the story, or being attacked alone. He quotes his twenty-two cases in the Helsingfor clinic, of which twelve were in both hands. In twelve the fourth or fifth or both fingers were involved. The others showed various modifications. In four of the families some hereditary history was obtainable. Involvement of four generations was found in one case.

Krogius states that Riedinger (1898) was among the first to show hereditary histories. He, however, would trace the somatic factor through sesamoid bone rests. Such are so infrequent as to render this conception very tenuous.

The Palmar Aponeurosis.—The developmental history of the construction of the palmar aponeurosis in man is still difficult to completely envisage. It is not the intention here to enter into the many uncertainties. It is not a simple connective-tissue sheet of unitary origin. For our purposes it is a compound of tendinous remnants from several phyletically more active muscles. The *palmaris longus* plays a large part in its construction. It may again be recalled that Dupuytren's critics, Malgaigne and others, claimed the contractions were of the still active tendons, chiefly of the *palmaris longus*. Naturally in those days the principles attendant upon phylogenesis and modifications of older structures were only beginning to be grasped. The embryologic superficial sheet of the antibrachial flexors contains the anlage for the *palmaris longus* and the *flexores breves manus superficiales*. Thus the modified superficial short flexors also may contribute their aponeurotic quantum to the palmar aponeurosis. Only the *palmaris brevis* in this

group of superficial flexors of older mammals is occasionally found in man. Hence the fourth- and fifth-finger predominance.

In studies by Grafenberg the human embryo shows evidences of a *flexor digitorum manus brevis*. Although much of this muscle would seem to join the deep flexors—*flexor digitorum sublimis*—some of its superficial layers also enter into the palmar aponeurosis.

Whether other muscles of the superficial layer, important in lower forms of many mammals, enter into the construction of the palmar aponeurosis, it is not necessary here to go into greater detail. It is enough for the purposes of this paper to be certain that the aponeurosis consists chiefly of fibrous connective tissue of tendinous origin from phylogenetically appreciable muscular tissues which at one time were largely under cortical voluntary and cortical and striatal spinal reflex activities. (The whole problem of "reflex grasping" need not here be more than mentioned as of behavioristic significance. Critchley, Schilder, et al.)

Kajava (1917) in a study on the phylogenesis of the *palmaris brevis* and the *flexores manus breves* muscles in mammals showed that in many lower forms (monotremata for example) whereas the *flexor brevis* muscles ran to four digits, in higher mammalian forms and up to lower primates the four and five fingers are alone so served, and that in the higher apes and in man these muscles are lacking. Only in anomalous rare cases can the *flexor brevis* be found running to the little finger. The *palmaris brevis* exists in higher forms chiefly as a superficial semi-muscular semi-aponeurotic flexor for the hypothenar eminence.

Grafenberg in his embryologic studies has pointed out that the *flexores breves manus superficiales* make up a fairly large and important muscular mass, which later is to be differentiated, during which some of the earlier mammalian utilizable muscle fibers fail as complete muscular structures but pass over into the construction of the fibrous bands of the palmar aponeurosis.

Thus Krogus came to the conception that phyletic hangovers, particularly of the short flexors, would account for the predominant involvements of the fifth, fifth and fourth fingers which is so evident and striking clinically. Thus the heredity factor would receive support and explanation.

He further would think of the slow contractile process as a

register of a tendinous regression of an undeveloped muscle anlage rather than a chronic-plastic inflammatory activity.

Our own more central dynamic conception could accept both processes as operative rather than one exclusively.

Krogius would summarize his study as being disposed to regard Dupuytren's contracture as due to developmental disturbances in the phyletic history of the superficial hand musculature (*Mm. flexores breves manus superficiales*). Since the palmar aponeurosis must be considered in part a derivative of these in various mammals, and also occurring in the musculature of the human embryo, the newly developed tissues which fundamentally induce the contractures may be referred back to embryonic rests of the same muscular sheath.

The conception is not to be understood that true atavistic muscles have developed which in the disposed individual resulted in a tendinous modification of the same—but that the process is so conceived that the musculo-tendinous connective tissue incorporated in the aponeurosis develops in later life directly into the contractures.

As may be seen, Krogius goes only as far as *description*. There is no dynamic conception anywhere that there is any "pull" on these shadowy remnants of previous pullable structures. The forces that once brought about physiologic and useful activity through muscular and tendinous structuralized experience now are capable of causing pathologic useless crippling, as unconscious "purpose" would reach back into the shadowy past and find only the remnants of what was once there.

In a manner of speaking, then, it may be important to say that certain voluntary contractile possibilities as in the hands (and probably by homology in the feet) of lower mammals up to lower primates and even certain higher primates, are passing from conscious muscle-tendon contractile activity to "unconscious" aponeurotic contractile capacity. In a sense such intermediary "conscious-unconscious" impulses will be more capable of producing results proportionate to two factors: The one somatic, and dependent upon the persistence of more musculo-tendinous tissue in those "heredity" families, and, the other, upon the nature of the development of the "grasping tendencies" of individual personality development. *This latter factor in its more detailed analysis is the newer, novel, or more*

completely developed conception which this paper would emphasize and offer supporting evidence from the psychoanalytic methodology.

ABBREVIATED SYNOPSIS OF CASE HISTORY

It is not my intention here to enter into details of the general situation for which I was consulted. By reason of necessary restriction of an all-round presentation of the case history and the consequent picking out of the particular "hand-system-complex function" this, a preliminary study, must be viewed as a fragment only. In a rough sense, by analogy, I can offer but slight strains of a disjointed melody which flows within the body of a symphonic composition.

Believing as I do that practically all of the manifestations of the bodily functioning, physiologic or pathologic, must be viewed as a whole, then no single issue can be thoroughly understood without this "as a whole" conception. It is, therefore, an arbitrary procedure to pick out the Dupuytren's contracture should it be considered apart from the rest of the personality of the individual who harbors it. It will be seen, I hope, that *this particular pathologic manifestation is a consistent developmental product of the inner life of this individual*. It is a product of his "Id," i.e., his deep unconscious, and its pathology, for him, and for *his case alone be it here emphasized*, becomes understandable. Even though I would thus avoid generalization and point out an individual pathology, the principle to be evolved, I believe, runs through most of the Dupuytren's contractures, even though other obvious factors, infectious arthropathies, syringomyelia, multiple sclerosis, spinal-cord or peripheral-nerve injury, etc., etc., accompany and may make possible the appearance of "Id" forces because of the loss of or hindrance to peripheral drainage factors. As I have previously discussed, *in extenso*, this coördinated emergent evolutionary picture of what has heretofore been set forth in parallelistic terms of somatic pathology and psychopathology, I shall refer this whole point of view to the interested by citation only.¹

¹ With DR. WILLIAM A. WHITE: "Principles Underlying the Classification of Diseases of the Nervous System," *Journal of the American Medical Association*, vol. 66, p. 781, 1916; also see in JELLIFFE, AND WHITE: "Diseases of the Nervous System," Fifth Edition, Lea and Febiger, Philadelphia, 1929; JELLIFFE, S. E.: "Paleopsychology; A Tentative Sketch of the Origin of Symbolic Function: *Psychoanalytic Review*, vol. 10, p. 211, 1923; "Neuropathology and Bone Disease,"

FIG. 1.



This is a picture of a patient of Doctor Bunnell's here reproduced, since my patient said it more truly represented his early condition, say at the age of thirty, than a score or more illustrations which I showed him. No one had ever taken a picture of his hands.

I first saw the patient in March, 1930. He was then fifty-two years of age. He came, through consultation, complaining chiefly of intolerable drawing sensations, chiefly in his arms. They were felt in the wrists, the elbows, the shoulders, also the back of the neck. The thighs and knees also had them. They were constant. There was tingling in the course of the nerves of the arms. The location of an, at times, "almost nauseating" tingling which was emphasized is shown here as complained of as of January, 1928. At times the finger-tips would tingle and have cotton-wool sensations, save when he lay down to sleep. His eyes bothered him also. He had drawing sensations there. He could not focus well.

The joints themselves were not stiff, he would explain, although he wanted constantly to "work them" as if to loosen them up or relieve him of the intolerable drawing-pulling feelings.

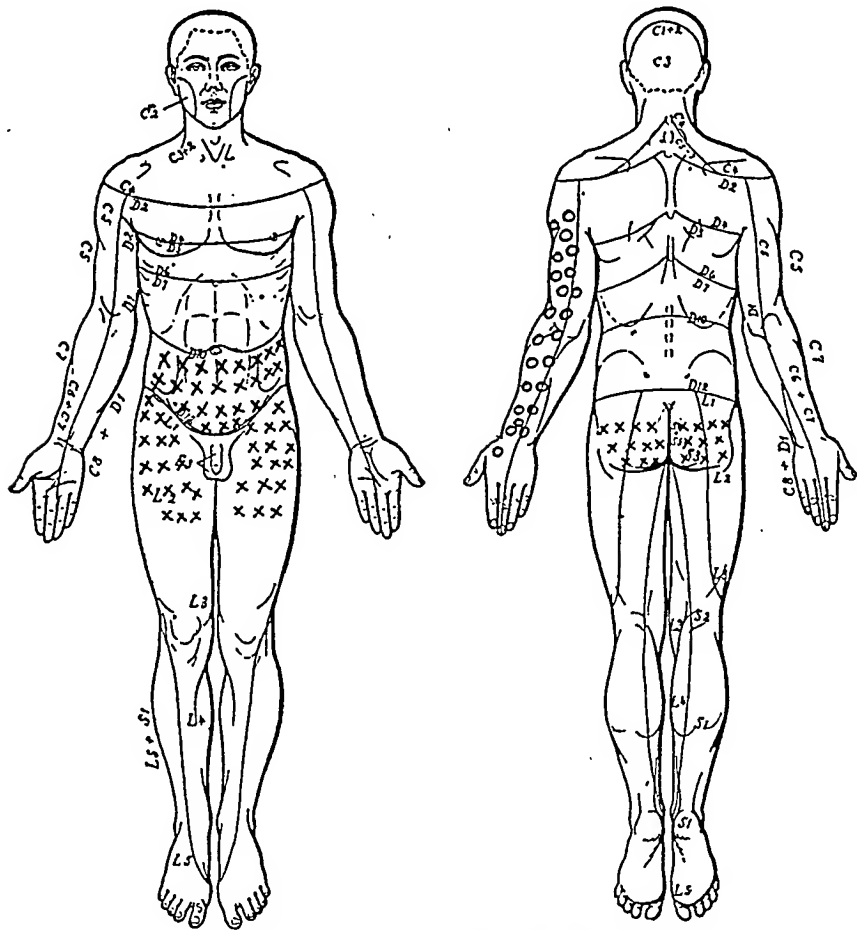
As far as could be learned, the "damned thing," as he expressed it, was of gradual evolution, was persistent, and was increasing. He had good days and bad days, good hours and bad hours. Certain attending factors here will receive further comment.

The eye symptoms apparently were the first, and it is possible although difficult to clearly pin down that these had an acute onset. This was in the summer of 1927 when he was salmon fishing in Canada. Here he had a "stomach upset" (?) with nausea. He awoke with acute retching, got up to urinate, was dizzy, things went around and around. He was forced to stay in bed, he thinks a few days. He is not sure but maybe he saw double at this time. At all events he felt "rotten" for a day or two. There was no headache recalled although he had had infrequent attacks of migraine with scotomata and nausea and headache—no earache.

Transact. of the American Neurological Association, p. 419, 1923; "Unconscious Dynamics and Human Behavior"; In Morton Prince Festschrift, page 231, Harcourt, Brace and Co., New York, 1925; an amplification of paper on "The Psyche and the Vegetative Nervous System with Special Reference to some Endocrinopathies," *New York Medical Journal*, April 5, 1922; "Somatic Pathology and Psychopathology at the Encephalitis Crossroad," *Journal of Nervous and Mental Disease*, vol. 61, p. 561, 1925; "Psychologic Components in Postencephalitic Oculogyric Crises," *Archives of Neurology and Psychiatry*, vol. 21, p. 491, 1929; "Vigilance, the Motor Pattern and Inner Meaning in Some Schizophrenics' Behavior," *Psychoanalytic Review*, vol. 17, p. 305, 1930; GRODDECK, G.: "The Book of the It," *Nervous Mental Disease Monograph Series*, No. 49; GRODDECK, G.: "Our Unknown Selves," London, 1930.

Three or four days later he had a "rotten dizzy spell." He thinks the tingling began about this time, possibly earlier, but it was hard to locate temporally because, from the old Dupuytren's contracture, he had always had a slight sense of pulling. Following the operations seventeen years ago (Doctor R . . .), and two

FIG. 2.



xx Location of almost nauseating tingling sensations.
 oo Pulling tingling drawing in both arms but were more constant in areas indicated. (March 10, 1930.)

years ago (Doctor P . . .), there were always peculiar sensory disturbances in the fingers.

His troubles continued. He was an inveterate woodsman, hunter, and fisher. He noted gradually advancing uncertainty in his wading the trout streams; the birds got away from his gun by reason of the blurred vision and focusing difficulties and slight

initial motor checking. He grew more and more annoyed with petty hindrances to his enjoyment, and his apprehension and hypochondriac self-involvement grew on him. He anticipated impending dissolution, cerebral hemorrhage, heart failure (he had some extra systoles) blindness, paralysis, rheumatic disability, etc.

He consulted competent internists, surgeons, neurologists, X-ray specialists, etc., as early as March, 1928. One set of diagnoses at this time was, psychoneurosis, neurasthenia, benign thyroid tumor, and Dupuytren's contracture. Complete internist, neurologic, X-ray, metabolic and biochemic study revealed no marked variables from established "norms." The complete report is unnecessary in this discussion.

Since this time to when I saw him in 1930 other similar investigations were all "negative" so far as structural alterations were definable. He has a slight right corneal arcus-like cloudiness. That "reversible" to "irreversible" processes were going on is incontrovertable. The "why" of such a judgment affords the nucleus of this study.

In March, 1930, the patient, as stated, was fifty-two years of age. He was married twenty-eight years; was a successful professional man. There was a daughter of twenty-three, a son of twenty-one, and another daughter of sixteen. His father had died at seventy, kidney, when patient was twenty-two. His mother had died at the age of eighty-four. She was restless, nervous and twitching. His father had some Dupuytren's contracture as had his father's mother, he thought. There was a sister two years older than he and a younger brother. There are no outstanding familial variables, save the very neurotic mother.

Only a very brief summary of his childhood and adolescence can be offered. He was a happy, active boy much attached to his highly neurotic and restless mother, who, with the unmarried sister, became strongly Christian Scientists. He was a possible bed-wetter. No other neurotic traits of childhood, save he used to sniff a great deal. He can recall the "habit" as early as seven or eight. He had many "colds" in the head from eight or nine to twelve or thirteen. He made good marks at a high-grade university, and took up his professional work, in which he has been progressively successful above the average. He always had a hankering for the woods—took fre-

quent week-ends and short holidays, rationalizing his extra interest in motor activity, sports, living in the country, *etc.*, as "healthful"; "being nearer to family"; and other well-accredited and wide-spread rational motives.

The unconscious material very early showed definite mother fixation factors. The father situation was not so quickly revealed, although it was soon apparent that the oral-sadistic pregenital phases of his libido situation were well invested.

The infantile oral-anal sadistic trends had developed chiefly along the motor pathway. Very briefly they were clearly separable into (1) an infantile cruelty phase and (2) the adult hunting, fishing, excessive motility, hustling, socialized, syntonic-get-together phases.

(1) *Infantile Phases*.—The sniffing and "colds in head" have already been alluded to. These belong in the nasal cathexis, displacements from behind-below to above-in front, *i.e.*, anal to nasal, as is so well known. Constipation was present. He also had some interesting sadistic plays when five, six or seven years old. He constructed a small guillotine with which he would chop off the heads of grasshoppers, *etc.* A little later he constructed a hangman's apparatus. He had a set of nine-pins with painted heads. There were the different types of men—merchant, minister, *etc.*; these he would hang with considerable childish gusto.

There were a number of important variants of these cruelty plays, too involved to enter into in this short outline.

Oral fixation on the mother—appearing in not infrequent dreams of "twin objects" (breasts)—had led to an equally interesting character development. At his mother's knee he learned many poems, songs, *etc.* This fixation became a social asset in that he remembered literally thousands of poems, songs, stories, *etc.* This tenacity of memory—this holding—could be dilated upon to a marked degree. Whereas it never developed to the "miserly" stage as is frequently seen, nevertheless there were an innumerable series of small holdings, graspings, which are of significance in the whole hypothesis of "grasping" as related to the "hand" situation.

Much more might be written about the infantile "grasping" features of the pregenital erotic areas, but such would belong to a complete psychoanalytic presentation, which this paper is not.

As the genital phase of adolescence was reached, the conflict of masturbation arose. To develop this theme adequately would require many words.

That remnant of the unsolved Œdipus Complex—as evidence the wish to castrate others (guillotine, hanging devices)—now threw up a hindrance to complete masturbatory development and gratification at the adult level. The sense of guilt was not particularly inhibiting in the Conscious when actual manustupration began at eleven, but the evidence is strong that a marked de-fusion of instinctive object activity took place at this time. Detailed consideration of earlier homo-erotic activities (seven, eight, nine years old) are omitted here, but the presence of such is noted as relevant to castration anxiety. Hence the displacement to and punishment of the left hand. The contractures began then in the left hand (twelve years). The “Id” would grasp with the right hand the Father Potency object with unconscious castration wish-intent, but a tyrannical Super Ego bearing down forces the displacement of libido, through denial, from right to left to the inner gratification of possession by grasping, thus subtly camouflaged. Thus the body is punished in true Pauline fashion. (The *lex talionis* principle “If thy right hand offend thee, cut it off,” etc.) Details of the persistence of this all-powerful grasping tendency, through repressed masturbatory inner urge, cannot be entered into here. One dream bit of evidence alone is offered. Its complete analysis belongs to another phase of this presentation.

“I am fishing in my favorite club stream, at the weir where the water is deep, just below the small falls. It is dark and the slightly foamy water is very attractive. The biggest fish are apt to be found in that place and I am anticipating getting some fine ones. Then in some manner I dry up the entire stream and I catch big trout in both my hands.”

To those but slightly acquainted with dream mechanisms the strong grasping tendency shows itself here at a pregenital level combined with the masturbatory urge. Analysis of the dream, among other things, showed the pregenital urinary cathexis (water fall—biggest fish, in deep pool) and the later masturbatory object investment (grasping trout in both hands). The large amount of energy

in the wish is adduced from the magic of drying up the pool. The relationship to the underlying Œdipus Complex is also obvious.

As to the wished-for Father Potency factor which also shows up at a magic or mystic phantasy level, hence theoretically heavily invested, one or two bits of dream evidence may be noted.

In one dream: "A half-horse half-man (*Centaur*) animal is *anticipating coitus*." (Other details omitted.)

This type of Centaur dream I have met with but rarely and thus far in my experience it has been found only in certain types of individuals who have in some more or less marked manner carried out some type of castration within their own bodies (*lex talionis*). With me it has been found in three instances in patients with multiple sclerosis, with two who showed a progressive myopia, in one boy, twelve years of age, with diabetes, and in one epileptic girl. In two criminals of the neurotic criminal type (Alexander), *i.e.*, those who carry out criminal actions in order to be punished, I have also had such dreams. The theoretical implications of the animal dreams I have gone into in some detail in a previous paper.¹

Leonardo da Vinci was the first great anatomist who really appreciated the muscle dynamics of standing. His drawings represent with faithful accuracy that the muscles utilized by a horse in rearing are the same as those used by man in rising from a stooping to an erect position and in keeping him erect.² I venture to assert that the "rearing Centaur" of the patient's dream life is an indication of a profound psychodynamic urge on the part of the patient to be greater than the father, *i.e.*, to possess in a surpassing degree the mounting capacity of the father, *i.e.*, have his infantile unconscious phantasied phallic power with the wished-for mother.

This particular patient never showed the interesting involvement of the penis found in other cases of Dupuytren's contracture which is here to be interpreted as related to this selfsame penis supremacy wish.

Since the earliest signs in this patient began at about the age of twelve, it is psychoanalytically interpretable that the masturbation displacement with its accompanying retribution reaction

¹ With BRINK, L.: "Rôle of Animals in the Unconscious," *Psychoanalytic Review*, vol. 4, p. 250, 1917.

² Cf. MURRICH: "Leonardo da Vinci, the Anatomist," 1930.

(*lex talionis*) afforded sufficient outlet for the repressed Œdipus situation. Just at what ages the fixations would tend to cluster in order to bring about the unconscious actual penis castration (by bending) details of the available histories do not permit of any adequate analysis. Should the opportunity offer, further inquiry concerning these unique case histories may be carried out.

One other feature of the Centaur position, or more properly speaking, the animal-coitus position, as an index of infantile theories of coitus, and also related to incompletely sublimated anal-sadistic phantasies, another dream may throw light upon this investment as bearing upon the "nauseating tickling" sensations of which he complained. In this dream, "*Coitus was being attempted from behind, but great care was being exercised [and this was emphasized by the dreamer in telling it] not to penetrate the anus.*" This is but part of the dream. Bearing on this infantile animal position material also were dreams of unmistakable character. "*Two dogs in such position but kissing each other in unmistakable human character, with almost clear glimpses of smacking lips.*"

The parts of the body which would be brought in skin apposition—*tactile skin erotism*—a large factor in this contractile palmar aponeurosis—are shown in the accompanying charts. (Fig. 2, page 194.) It is of psychologic import to note that in these "nauseating sensations" the patient is both subject and object. That the vulgar jargon should have an adequate phraseology for this retributive activity is not without considerable significance.

It would lead to too great piling up of detail were all of the situations relative to great impatience, at times childish, irritable behavior when thwarted, even in minor games of backgammon, bridge, etc.; ever-present persistent and markedly titanic desires to anticipate, to hurry, to get hold of things before it were possible, or lest he be thwarted. Jink's, and other gestures, oaths, rituals, superstitious observances galore exemplify the infantile stages of libido cathexes which have had a partial liberation through the grasping, holding activities through the hands but by reason of inadequacy of performance at really creative levels have flowed into the vegetative effectors and old connective-tissue metamorphic products of what were in lower animals tendinous capacities for such holding, grasping, reflex activities.

John Fothergill, Caleb Parry, Wilks and the late Sir James Mackenzie.

While the morbid process underlying a disease is unknown, speculative pathology must stand in the place of knowledge. This is true now as regards migraine, as it was at one time true of asthma and of paresis, and is still true of multiple sclerosis. For instance, Timme believes the sella turcica is always deformed in migrainous subjects, that it is always either over-small or closed from above, and that pituitary swelling produces the headache by capsular distension and the subjective visual symptoms by pressure on the optic chiasm. It is proper to point out that migrainous headache bears no resemblance to the deep-seated central pain of pituitary adenoma nor are the zigzag fortification spectra of migraine ever produced by any of the known pathologic conditions affecting the crossing of the optic nerves; further, the many thousands of skull radiograms taken in war of normal men revealed many types of sella deformity without symptoms. It has even been suggested that the usual alleviation of migraine symptoms in the fifth and sixth decades of life is due to sellar erosion consequent on a lifetime's periodic pituitary pressure! Undoubtedly, persons afflicted with migraine often suffer gonadal abnormality, hyperthyroidism and endocrine disturbance by thymic persistence, all related possibly to disordered pituitary function. However, such disordered function does not necessarily emanate from *primary* hypophyseal pathology—we have seen all these things appear as *neighborhood* pituitary symptoms—for instance, in encephalitis and in localized luetic inflammation of the meninges; and a localized edema of the basal membranes could and, in my opinion, does give rise to such endocrine errors as from time to time complicate the symptoms of this disease. Such a notion therefore makes it necessary to examine the current theory of cerebral vascular spasm as accounting for the migrainous picture. When this idea was first put forward physiologists believed not at all in the existence of vasomotor cerebral nerves; Gaskill's observations, however, have shown this view to be unsound and Penfield has lately demonstrated such nerves in tissue. It would therefore seem certain that vascular spasm can occur in the brain and its membranes, but migraine with dilated vessels in forehead and retina is frequent enough, and it is not easy to follow

the dynamics by which the totality of migraine could be brought about by arterial spasm alone. This symptom complex is most varied in character. The one-sided headache is in itself a fantastic-appearing ailment for which there is no analogue in medicine, other than perhaps the localized headache of chronic fibrinous meningitis. By spasm of what artery can one explain the paralyses of ocular muscles coming on subacutely in the course of the headache and often needing days, and occasionally weeks, in which to recover? When I was a House Officer one of my colleagues came to breakfast totally alexic, partially aphasic, with a right homonymous hemianopia, and a violent left-sided headache which lasted more than twenty-four hours, after which all symptoms ended abruptly with violent vomiting. This physician had had many similar attacks of a less pronounced and dramatic character. The zigzag flashes or spheres of light seen by the migrainous patient at the outset of a seizure are often on all fours with the phenomena produced by a discharge of the visual cortex in a calcarine fit, and the loss of the power to recognize written symbols and still more blindness in the visual fields away from the pain is in total agreement with our knowledge of such phenomena produced by irritation and pressure on the visual areas in the brain. It is almost a commonplace for attacks of migraine to be associated with contralateral numbness and tingling with the extremities and Osler described a patient in whom the headache synchronized with a passing hemiplegia with alteration of reflexes characteristic of organic disease. We are indebted to Oppenheim for a description of a case of migraine which was almost always accompanied by ataxia of both limbs and station and other evidence of localized cerebellar disturbance.

Precisely similar signs and symptoms appeared in a patient seen by me in consultation with Dr. W. L. Niles: acute cerebellar disorder with severe headache and drowsiness appeared in the course of a severe attack of urticaria, and vanished with the disappearance of the swellings in the skin. Indeed, I lean very decidedly towards the belief that edema within the skull involving chiefly the meninges and especially their foldings and angular reflexes, and less severely the brain tissue, often initiated through intoxication, by foreign protein or from the gastro-intestinal tract,

is the method whereby the typical headache and localized cerebral symptoms are brought about.

It is in no way probable that the headache comes from direct brain involvement for the cerebral tissue would seem to lack sensitiveness; needling the brain under local anesthesia is painless but pinching or stretching the meninges or meningeal vessels is agonizing.

In fine, it would seem that edema of the skin may appear as urticaria; edema of the brain as in alcoholic or uremic poisoning produces fits, and edema of the cerebral meninges with especial pressure in the meningeal crevices produces the localized headache and the local cerebral symptoms of migraine.

MANIC DEPRESSIVE PSYCHOSIS IN CHILDHOOD*

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ONE of the notable developments in medicine in recent years is the growing appreciation of the extent to which problems of illness, confronting the physician primarily concerned with somatic medicine, intermingle with psychiatric disorders.

In both medicine and psychiatry, it is being emphasized that in the understanding and treatment of human illness one must consider the "individual as a whole." The truth of this proposition is becoming more evident, as our information increases regarding genetic factors and constitutional qualities in determining the life reactions of the individual. The understanding of the individual thus becomes a fundamental matter in good medical practice. In the technical acquisition of this understanding, the experiences and concepts gained in the field of psychiatry must be utilized. No physician has better recognized this aspect of medicine, in theory and practice, than Doctor Barker to whom the contributions of this volume are dedicated.

There is another aspect of this need for the understanding of psychiatric disorders by the physician which warrants emphasis, and this is that the practitioner of medicine has the opportunity of seeing the beginnings of psychiatric disorders in periods before the psychiatrist is brought into the situation. Usually when the psychiatrist is confronted with a mentally-disordered patient, the disorder is well advanced and in the nature of the problem therapeutic possibilities are regrettably too often ineffective. Often when one looks back into the early history of a psychiatric case, it is possible to recognize manifestations which are in direct relationship to the later stages of the disorder and believes that if these had been understood in their significance something might have been done to avert a later serious situation.

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These matters are of special importance to those whose medical practice deals with children. In a considerable number of mental disorders, the etiologic determination seems to be by reason of certain qualities of constitution. This being so one would expect that significant manifestations of these abnormalities of constitution would appear in the early years of life, at times when the care of the individual is a responsibility of the family doctor.

Even if there is no specific therapy as yet known, that will bring about a complete restoration to health, it is obviously worthwhile to know this. In such instances, if the situation is correctly comprehended, much can be done in instituting a hygienic life program that may be effective in preventing further progress and disaster. There are many analogies to this situation in internal medicine, *e.g.*, diabetes, hemophilia, vascular hypertensions, *etc.*, disorders in which curative therapy is as yet unknown but which by proper life regulation a good measure of continued health may be assured.

Interest in the psychopathologic disorders of children has largely been centered in what are generally classed as "behavior problems," and the numerous pathologic manifestations of the psychoneurosis, psychopathic personalities, and mental deficiency. Much has been learned regarding these and has found practical application in wide extent, in services for child study, in behavior clinics and special organizations in schools and community. Less, however, is known regarding the occurrence and clinical manifestations of those more formalized clinical disorders which are classed as psychoses such as dementia praecox and manic depressive psychosis.

In respect to dementia praecox, there has been gained a considerable knowledge of the childhood characteristics of those who later develop this disorder. Regarding the early life history and the personality reactions of those who develop manic depressive psychosis, our knowledge is meager. Reasons for this seem to be that it has been supposed that manic depressive psychoses are extremely infrequent in children, or the manifestations of the disorder are so mild that they do not come into institutions, or where abnormal reactions occur they are overlooked or regarded as of no significance and as unimportant manifestations of average childhood behavior.

The age of greatest frequency of the occurrence of the first attack of manic depressive psychosis has been given by Kraepelin in the

age period 15-20. Among over 900 cases of this disorder Krapelin¹ found only .4 per cent. occurring before the age of ten. Lange² in his comprehensive discussion of manic depressive psychosis comments on the great infrequency of the disorder in childhood and that even in the histories of those developing the disorder before the twentieth year, it is rare to find that there have been any manifestations of the disorder in childhood years.

In a review of our own material at the Psychopathic Hospital at Ann Arbor, we have found that attacks in earlier years are more frequent than had been thought by others. In a series of 100 cases of manic depressive psychosis in which the first attack occurred before the twentieth year, there were 5 per cent. who had a first attack before the age of twelve. The fact that in this disorder the rule is that other attacks will recur during the lifetime of the individual, makes it important that the early attack should be recognized in order to formulate efforts towards preventing their recurrence.

CASE I.—F. O. First attack at age of ten.

F. O., a girl, twelve years of age, entered the clinic in a state of hyperactivity; exhilarated mood, and an extreme degree of talkativeness. She came of a family showing several instances of mental disorder. Her paternal grandfather was in a state of melancholy the last six years of his life. The paternal grandmother had during her life attacks of rheumatism and at the age of sixty-four was mentally disordered and died the following year from arteriosclerosis. The maternal grandmother after the age of fifty-four continued throughout her life in alternating states of depression and elation. The patient's father was free from mental disorder but his two sisters at times during their lives had recurrent periods of depression. The mother of the patient had alternating periods of depression and excitement, and her sister suffered from mental disorder.

The patient was the youngest of four children, one of whom was somewhat dull and stammered. She was a healthy child doing well in school until the age of ten, when she became irritable and inactive. She would not go out from the house, and was afraid that people were watching her. Things about her seemed unnatural and she expressed the feeling that she did not belong to this world. There was little spontaneous talk. This depression continued for seven months and then she passed into a state of excitement. She talked excessively, her thoughts were flighty, and she sat in peculiar positions. For the next four months, phases of depression and excitement alternated every two weeks. There then occurred a period of depression which continued for three months, and then following an acute disorder of the ear, she regained her normal level. A month later a period of depression recurred and from then on until her admission to the clinic at the age of twelve, she continued in alternating brief periods of depression and excitement.

The examinations in the clinic disclosed no physical pathology. Menstruation had not then appeared. For three weeks she continued in a typical manic excitement. She was extremely active and her mood was elated. She talked incessantly, her speech productions showing a flight of ideas. This excitement continued for seven weeks when it began to gradually subside. Her weight began to increase one week after her admission, and after seven weeks when she was discharged as recovered, she had gained fifteen pounds.

At home she soon again became depressed. This continued for two weeks and from then on she continued in normal mental health for two years. During this period the first menstruation occurred.

At the age of fourteen she again entered the clinic in a state of excitement which developed after a brief period of depression after a failure in her school work.

Her condition at that time was one of typical manic excitement. She was exhilarated in mood, distractible in her attention, boisterously overactive, and continually talking. Her speech production showed a typical flight of ideas and sound associations. Her excitement continued for about nine weeks at a uniform height and then rather abruptly passed off without being followed by a depression. Fourteen weeks after the onset of her excitement she had regained her normal mental health. Her weight began to rise soon after her admission and by the time of her recovery she had gained twenty-two pounds.

She was cared for at home until the age of nineteen when she again developed an excitement which led to her admission to a state hospital. Her family state that during this interval at home she had many mild alternating states of depression and exhilaration. This latter attack of excitement passed off after a few weeks when she had regained her normal health. In the year following occurred another attack of excitement of brief duration. Following this she remained well for eight years when another attack requiring hospital admission occurred. In the years following there is a history of many brief periods of depression and excitement.

The genetic relations of this case, F. O., is one that frequently occurs in manic depressive psychoses. Of all the psychoses, this disorder shows the highest frequency of heredity factors. In critical studies of this question it has been found that in 85 per cent. of cases of manic depressive disorders there is an heredity of nervous or mental abnormalities.

The line of the transmission is usually direct and in this respect the heredity of this disorder differs from dementia praecox where the tainting predominantly occurs in indirect and collateral lines. Where psychoses occur as tainting factors it is the rule that these are usually manic depressive disorders. In this case there were heredity factors in both paternal and maternal sides; and the mother had the same disorder. It is not uncommon to find in manic depressive psychosis that one or the other parent had the disorder, but in

dementia praecox it is most exceptional to find a parent having dementia praecox.

In the genetic relations of the psychoses there are problems presented which also have an interest for pathology and internal medicine and emphasize the interrelation of psychiatry with constitutional somatic disorders. In this case the maternal grandmother in addition to a psychosis had rheumatism and died from arteriosclerosis. There also were several other members of the family who had cardiovascular disorders.

It has been found in the studies of manic depressive families that arteriosclerosis occurs with a frequency that seems to suggest some connection of the etiology of this disorder with that of manic depressive psychosis. This significance is also emphasized in the fact that the constitutional somatic type is the same in both disorders, and the most frequent cause of death in manic depressive psychosis is a cardiovascular disorder.

In this case there seem to have been no peculiarities of personality until the outbreak of the disorder. The first attack at the age of ten was a depression, and the subsequent course was characterized by frequent attacks of brief duration some of which were entirely manic excitement while others were of double phase suggesting a circular type of course.

CASE II.—J. C. Onset at age of eleven.

J. C., a boy, aged fifteen, entered the clinic August 10, 1929, in a state of excitement.

It was impossible to ascertain the genetic situation in his family owing to the informant's lack of knowledge of its members.

In his early childhood he was described as being active and lively. In school he was rather dull, at the time of his hospitalization he was in the ninth grade. In this year he failed in one of his studies, and on one occasion was expelled for a period because of "obscenities." He is said to have had some of the diseases of childhood with complete recoveries. For a time during his earlier years he was a nail-biter and recently, when mentally ill, he occasionally was enuretic. For a time it was observed that before going to sleep he was excessively restless.

As he grew older his disposition changed from the activity characterizing his earlier years. He became subdued in his reactions, he kept much by himself, had little to say, and was self-conscious and shy.

At the age of eleven he had his first attack. For a period of eight days he was depressed, complained of a choking feeling in his throat; he cried much and was profane. He expressed the wish to die, threatened the life of his sister, and to kill himself. After this period he abruptly regained his usual health.

A second attack occurred at the age of thirteen, when he again complained of choking. This was one of excitement, he was hyperactive and boisterous in his behavior; during this he was excessively talkative. After ten days he returned to normal. During the next two years he had several brief milder episodes of excitement characterized by hyperactivity and increased talk. With no premonitions on July 4, 1929, he suddenly became overactive, tore his clothes, destroyed things about the home, was extremely irritable, and talked continuously. After twelve days this condition somewhat subsided and then after three weeks, during which period he did not quite reach his normal level, he again became boisterous, excited, talkative, and irritable.

In this condition he entered the clinic. Examinations of his physical and neurologic status showed no pathology. In an intelligence test taken after recovery he scored an I.Q. of 79. He was clear in consciousness and orientation. He was extremely overactive, playful, and at times boisterous. His attention was distractible. He talked in a rapid, impulsive manner, his output of thought was rather narrow in its range but at times he showed a definite flight of ideas. In general, his mood was euphoric and at all times there was a pronounced irritability. There were no hallucinations. His excitement continued at about the same level and then after six weeks from the onset suddenly passed away with a return to his usual mental health. In the year following he had several minor attacks of excitement, which did not lead to hospitalization.

In this case of J. C. nothing is known regarding the heredity influence. In his early life, he was a minor problem of bad behavior. It is of interest to note that there were neurotic manifestations in his early years such as nail-biting and enuresis. Such traits are frequent occurrences in children who are of psychopathic make-up.

The onset occurred with an attack of depression at the age of eleven. While his dominant reactions were those of a depression, there was also an irritability which gave the course of this attack a somewhat mixed character.

In the further course there were numerous brief attacks of abrupt beginning and ending.

CASE III.—M. G. Onset at age of twelve.

The boy, aged twelve, entered the clinic October 27, 1926, in a state of mental depression, the onset of which occurred eight months earlier.

The mother of the patient at the age of thirty-three had an attack of depression of a manic depressive character with complete recovery after three years. Her father at the age of fifty-eight developed a severe excitement with extreme overactivity and manic speech. The occurrence of expansive ideas, and a positive Wassermann reaction on the blood with death after three years, led to a diagnosis of general paresis. The entire course of his disorder was characterized by manic activity and thought with an exuberant mood.

The patient was the second of three children and was in good health and showed no mental peculiarities until his present attack began. There was no

backwardness in school, and in personality he was a friendly, apparently normal boy.

In February, 1926, at the age of twelve, he had two convulsions following injections of diphtheria antitoxin. He continued in a somewhat nervous state for eight months when he became obsessed by a fear that he had been poisoned, and in reaction to this he refused to eat. He was afraid to touch the door knobs because he might be poisoned. He was always unhappy and troubled. At night he cried much and often talked of dying. At times he spoke of a feeling as if bugs were crawling over his body. This state continued until his admission to the clinic on October 27, 1926. Physically he was in somewhat poor nutrition and the thyroid was a little enlarged. No secondary sexual development. There was no neurologic pathology.

He was clear in consciousness and orientation and there were no hallucinations. The most outstanding feature was his emotional depression and slowness of response. He usually cried when one spoke to him, especially when talking of his illness. He rarely spoke spontaneously and then only in brief remarks. There was always present a fear of being poisoned by the food or his clothing.

Two weeks after admission his weight began to rise. For two months there seemed to be little change in his depression or fears and then both rapidly disappeared. Ten weeks after admission he had entirely recovered. Subsequent information showed that he continued well for four years and then at times had periods which were described as nervous.

In the foregoing case the heredity situation is much like the case of F. O., since his mother and grandfather had manic depressive disorders. The first attack occurred at the age of twelve and while this was dominantly of depressive type, it had also the character of a compulsion neurosis. This intermixture with psychoneurotic reactions has been observed in a number of our cases of manic depressive psychosis occurring in early years.

The duration of the attack was longer than in the other cases cited but the subsequent course was better in that there was a long free interval before the other attack.

CASE IV.—M. W. Onset at age of ten.

M. W., a girl, aged thirteen, entered the clinic July 7, 1928, in a state of mental depression which had been present in varying intensity for three years.

The mother of the patient at the age of twenty was in this clinic in a state of severe manic excitement followed by a brief period of depression. Recovery was complete four months after the onset. Subsequently she had numerous brief attacks of excitement. In the further years of her life she had numerous brief attacks of manic depressive psychosis. Most of these were states of excitement. There were others in which she was depressed and in one of these she committed suicide at the age of thirty-one. There were no other known instances of mental disorders in the family stock.

From her earliest years she was regarded as a peculiar child. She was stubborn and gave way to impulsive outbursts of temper. As she grew older she

became a serious, sober, and unsociable personality. She made few friends, and always seemed to be unhappy.

She bit her nails and sucked her thumb and after the age of ten, when her menstruation was established, there was frequent onanism. Owing to poverty and the frequently occurring mental disorder of her mother, her home environment was bad.

At the age of ten she worried over her health. She feared that she had tuberculosis and that her body was shrinking. A frequent expression was "I am rotting away." On a number of occasions she complained of choking, and that sometime this would cause her death. At one time she felt unable to walk with one of her legs. After a few months she improved to a degree which enabled her to return to school. The following spring she again became unhappy and troubled. The old fears of tuberculosis and of choking returned. There were some remarks that suggested hallucinations. "People talk about me."

She became careless of her personal appearance and had long periods of boisterous unmotivated laughter. Much of the time she was slow in response. There were long periods when she sat quietly without talking. More recently she spoke of electricity charging her body and the automobile in which she was riding. She spoke of wishing to die and to be out of her misery. At times there were impulsive outbursts of destructiveness. Throughout all of this period she had an intense fear of dying and of having tuberculosis.

In this condition she entered the clinic on July 7, 1928. Physically she was a stocky and somewhat overdeveloped girl for her age. Examinations revealed no somatic or neurologic pathology.

Mentally she was clear in comprehension and orientation. Her reactions were those of an apprehensive depression. She was tense and troubled.

In her general behavior she was tense, and dominated by an apprehensiveness of harm. Her consciousness was clear, and there were no hallucinations. Her output of thought was a little reduced and her remarks showed her apprehensiveness. "The building was on fire. Her father had tried to get rid of her by filling her full of electricity. She was suffering from a contagious disease which destroyed those about her." A week later she was less active and talkative. Much of the time she lay on the bed with eyes closed, showing no spontaneous interest. She walked with extreme slowness. There gradually progressed a deepening stupor, she remained in bed, refused to speak, kept her eyes closed, and resisted passive movements of her limbs. It became necessary to feed her with the tube. This deep stupor continued for eight weeks when she became more active in her interests, at times would smile and began to talk and eat in a normal way. She gave an accurate account of what had happened round her while she was stuporous. Her improvement progressed rapidly, all apprehensiveness and uncoöperativeness disappeared. Her weight curve paralleled the course of her mental pathology. During the first weeks of her illness she lost seventeen pounds; even before there was any evidence of a lessening of her stupor, her weight began to increase and in the last eight weeks of her hospitalization she gained thirty-two pounds. Four months after the beginning of her illness, she returned home in apparently normal health. For about two years she continued well, and then occurred another attack of depression which brought her into a state hospital.

In the foregoing case, there is the direct heredity relation of manic depressive psychosis in parent and child. From earliest life she was a peculiar child. Neurotic manifestations were present in early childhood and during the later course of her illness.

It is of interest to note the worried reactions she had regarding her physical health in the early phase of her illness. While worries of this type are common in youth, it has been suggested by those who have studied the early manifestations of manic depressive personalities, that this may sometimes be indicative of a dispositional tendency to depressive reactions such as characterizes the manic depressive constitution.

The first period of her illness differed from that of the other cases in this series. Instead of a sharply differentiated attack of brief duration, there was a prolonged depression with variations from her tenth to thirteenth years. While the dominant clinical reactions were those of depression, the course and symptomatology were atypical. There were during the entire illness and especially in the attack when she was under observation in the hospital, reactions of a schizophrenic type. These were the episodes of unmotivated laughter, the delusions of influence, and the negativism during her period of deep stupor. Notwithstanding the prominence these had in phases of her illness, the diagnosis of an atypical form of manic depressive psychosis seems correct in view of the genetic history and the course of the disorder.

CASE V.—N. McD. Onset at age of ten.

N. McD., a boy, aged eighteen, entered the clinic on October 27, 1926, in a state of mild depression.

He came of a family in which mental disorders of a manic depressive type were present on the paternal side in three generations. The paternal great-grandmother, grandmother, and her sister were hospitalized for manic depressive psychoses. A paternal cousin, the daughter of a cycloid mother, had an undiagnosed mental disorder. On the maternal side, the daughter of a half-sister of the mother committed suicide.

The patient was the youngest of three siblings. At the age of eight he was an overactive child, excitable, and was a difficult problem in the home. He had from earliest years been enuretic. In school he did badly and withdrew when he reached the ninth grade at the age of sixteen. In personality he was mischievous, sociable, and well liked.

In 1918, at the age of ten, following an attack of influenza, there was a period of four days in which he was overactive, singing loudly, and danced about the house. He continued well until the age of seventeen when, following what

seemed to be a physical illness, he became overactive, distractible, euphoric in mood, and expressed expansive ideas. This phase was of brief duration and was followed by a period of stupor lasting about two weeks. There then occurred a sudden change to a state of excitement lasting three days and then an abrupt return to normal health. Two months later occurred another period of excitement with recovery after ten days. Two other brief attacks of excitement followed during the next six months, with several weeks' intervals between attacks in which he seemed quite normal. In October, 1926, he became inactive, slept much of the time, talked but little, and was morose and irritable. At this time he came under observation in the clinic. Except for the enuresis, the physical and neurologic examinations revealed no pathology. In general he was inactive, slow in his reactions, and unproductive in thought. He was irritable, complaining of his hospitalization and disinterested in his surroundings. He described his present condition as an attack of sleeping sickness and that similar attacks had come on him at various times in the past. There were no hallucinations or delusions. This stupor with irritability continued for two weeks when he became more active and free from irritability. Since leaving the clinic he has, with the exception of a brief period of stupor in 1927, continued in good mental health.

In this case of N. McD., there was an unusually heavy heredity tainting by manic depressive psychosis through three generations.

Throughout his childhood, he manifested abnormalities of personality and had a long persisting enuresis.

The first attack occurred at the age of ten, and directly followed an attack of influenza. This was a hypomania and lasted the brief period of eight days. From the age of seventeen to eighteen he had numerous attacks of brief duration, and of abrupt development and termination. The majority of the attacks were manic, some were depressive, and others of a circular course. The later attacks were somewhat atypical in the prominence of the irritability and ill humor.

In regard to the character of the attacks of these childhood cases of manic depressive insanity, and whether these differ from disorders of adult years, it is generally commented that the attacks tend to be of brief duration with abrupt beginning and termination.

Friedman,³ in 1909, in a contribution dealing with the affective disorders of children, separated the various types of course which this disorder follows, into three groups:

1. Periodic psychoses of characteristic form, in which a relatively large number of short attacks of depression or excitement follow one another immediately, so that there are relatively brief intervals of freedom before another attack begins.

2. More frequent are atypical depressions and excitements which closely resemble those occurring in later years, but are not to be classed as true psychoses. They occur in children of nervous endowment, as a result of emotional perturbations. After a short duration of a few weeks, they pass off and leave no after effects on the future life. These he designates as "psychopathic reactions."

3. There are other cases of mild melancholia and mania which are true psychoses and occur usually as single attacks in childhood. They last on the average only a few weeks. The clinical and prognostic importance of these is great, as they are precursors of the periodic psychoses of later years.

All of the cases we have cited in this series seem to belong in the first of Friedman's groups.

It has been usually observed that the first attack is of depression. This was true in four of our cases. Usually the depression or excitement is less severe than in cases of later years. This was true of all of our cases except that of N. W. The depression was characterized by emotional sadness, psychomotor retardation, limited thought productivity, and with no tendency to any prominence of delusions. The subsequent attacks uniformly were more intense and severe than the first.

In these early cases of manic depressive psychoses, dispositional constitutional factors stand out conspicuously. This is noted in the frequency and extent of heredity tainting in the families of the patients and in the prominence of psychoneurotic reactions of various sorts.

In one case no adequate information regarding the family was available, but in the other four, psychoses had occurred among other members of the family. In all cases the transmission was in the direct line and the disorder of the ancestor was manic depressive psychosis. Three of the patients had a parent whose disorder was of this type. In three of the cases manic depressive psychoses occurred through three generations.

Four of the patients had psychoneurotic reactions either before or during the attack. Two of these were enuretic; another was an habitual thumb-sucker, and nail-biter, and one had convulsions. During the course of the attack F. O. complained of feelings of unreality. J. C. and N. W. had choking sensations in the throat. M. G.

had obsessions, phobias and compulsive actions. M. W. at one time had an hysterical paralysis of one leg.

While psychoneurotic reactions are not infrequent among the psychopathologic manifestations of children, there sometimes occur cases in which at one period the disorder seems to be a psychoneurotic reaction and a subsequent attack a definite manic depressive episode.

This is illustrated in one case, not included in the series, in which the first attack at the age of five seemed to have been an obsessional compulsion neurosis, and a later attack at the age of nineteen, a depression of a manic depressive type.

N. W., at the age of three, had for a brief time what was called teething spasms. At the age of five, following an attack of whooping cough, she was depressed and unhappy. She would follow her mother about telling her "how much she loved her but the tempter told her to kill her mother." This lasted for three weeks, and from then on until her nineteenth year, she was a cheerful, well-balanced personality. At that time, during the holiday season, for a few weeks she was anxious and troubled and definitely depressed. She complained of feeling ill, that she could not do her work. She remained at home inactive and unhappy. She was afraid she might commit suicide or kill her mother. In this state she entered the clinic in February, 1925. There was present a mild nephritis but otherwise physical and neurologic examinations were negative. The depression varied, on some days she was cheerful and active but for the greater part of the time she was troubled by unhappy thoughts and self-criticism. After a month she entirely recovered.

Unfortunately there is lacking in the cases of this series as much knowledge as is desirable regarding the general personality qualities of the child in the years preceding the first attack. This is an aspect of the problem that is of great prognostic importance, not only for the early cases of this disorder, but also for its contribution to the etiology of cases developing in later life.

In this connection the question arises as to whether the tendency to worry unduly over matters of personal health, which is not infrequent in children, or where prolonged variations in moods or episodes of hyperactivity are significant as evidences of a cyclothymic temperament.

In three of the five cases of this series, comments were made by their parents of various personality peculiarities. One child was unusually stubborn, one was an unusually serious girl, another excessively active, and a difficult child in the home and school.

While the cases assembled for this discussion are too limited in number to permit of generalization or extended conclusions, they direct attention to the fact that these disorders are more frequent than had been previously supposed. In general they present a fairly well differentiated clinical group. The prognosis for recurrence of the disorder is severe. Their recognition for questions of prognosis and mental hygiene, is important not only for the psychiatrist, but for the physician in family practice and especially those concerned with children.

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EPILOIA-ADENOMA SEBACEUM WITH EPILEPSY (HYPERTROPHIC TUBEROUS SCLEROSIS)

By E. BATES BLOCK, M.D.

Atlanta, Georgia

PATIENT aged nine years and one month. Female. Unconscious spells, severe headache. Father died aged twenty-four years, typhoid fever—died six months before birth of patient. Mother living and well. Mother had no miscarriages. Tuberculosis negative. Malignancies negative. No nervous or mental diseases.

Patient was born full term—no instruments used—not jaundiced at birth. Sat alone, cut teeth, walked and talked at normal age. Had whooping cough at age three years. No accident, injury or operation. Had earache about eighteen months ago in right ear. Has had only very occasional sore throat. No tonsillitis. Eruption on face since age two years—small red pimples. Breathes well through nose. Teeth good, irregular. Had fever for two weeks at age four years. No rheumatism. Is in third grade at school and promoted each year except first grade.

At age fifteen months had first attack—was sitting in grandmother's lap—fell backward—eyes rolled upward—hands were drawn—lasted only a few seconds. Had these attacks—one or two a day—for about two months. Was taken to doctor and had no further trouble until about three months ago, then began having them again. Had an attack each night about two hours after going to bed until October 31, when patient had convulsion in day-time. Began about two weeks ago to complain of head swimming. Always knows when attacks are coming on now by head swimming and with the attack the right eye jerks, and drawing in right temple. Patient makes a crying noise while the attack is on. Says she has pain in right side of head while the attack is on. For the last four days has had the attacks oftener. Had ten attacks on Tuesday, November 9—on Wednesday had fourteen attacks and yesterday and today the attacks came every fifteen minutes. Attacks are getting closer together. Had an attack while sitting by my desk

but was not totally unconscious—right eye quivered and hands drew up to body but no muscular jerking. Would have fallen had she not been in mother's lap. Complained of head being hot after the attack had passed off. An attack in my presence started by saying, "Oh, mama," groaning, fretting sound, flexion of right elbow, wrist and fingers, quivering of right eyelid, narrowing of right palpebral fissure—was not unconscious. Pupils are very dilated between attacks and did not change in size during attack. In attack her face turned to left and eyes looked to left but when requested to look at my finger she turned both eyes and face to right.

Patient had two spells in office four minutes apart. Face and eyes turned to left both times. Both arms drew up in first but not in second spell. Flickering of right eyelids in each spell. Third spell at four minutes' interval. Dizziness and swimming in head for a month. Spells began to get worse on October 31, when they started in day-time. Before that they were all at night in her sleep. She always knows when the spells are coming on. The first symptom is a feeling of twitching in right eyelids and is felt before it becomes visible to examiner. Whines, grunts and says "Mama" in fretting voice. The muscular drawing is not always the same. Heart is 37 to one-quarter minute during a spell. The adenoma sebaceum started at age three years. The eruption is on chin and cheeks, nose, and slightly on forehead. Remarkable bilateral symmetry. The adenoma turn red during the spells and remain red for a few minutes after the cessation. Never any spells during sleep but has them when awake at night. Says that when one is coming on her it wakes her up. No attacks from November 29, 1926, until March, 1929, on 15th, 16th, 17th and 18th and on April 9 and 11 and none since.

Neurologic Examination.—Emotional state—nervous, apprehensive. Fears doctors will hurt her. Cries easily. Psychomotor—walks about—waits on herself. Headache—once every week or two for a month. Sleeps well. Dreams—none.

Cranial Nerves.—(1) Perfume R + L + Asafoetida R + L + Cloves R + L + Mint R + L + (2) Eye examination by Dr. F. P. Calhoun—"Vision without glasses was 15/15, pupils round, equal and active. Motility good, tension normal. Under homatropine her refraction was as follows: + 1S — 15/15 in each eye. Less + 25 was ordered for constant wear. I doubt very much if this hyper-

opia is the cause of the facial twitching and her other symptoms but I think the glasses should be worn. Discs are round, pink, with normal rings and deep physiologic cups. Retinal vessels are normal. The retinal, choroid and macular regions are likewise normal." (3), (4), (6) Pupils equal and react to light and accommodation. No nystagmus. Muscles good. (5) Motor and sensory good. (7) Moves well. (8) Hearing both ears twenty inches. No paresthesia. (9) No nausea. No dysphagia. (10) No vomiting. (11) Moves well voluntarily. (12) Protrudes straight and moves well in all directions.

Taste.—Rt. Ant. acid + Sweet + Bitter + Salt +
 Lt. Ant. acid + Sweet + Bitter + Salt +
 Rt. Post. acid + Sweet + Bitter + Salt +
 Lt. Post. acid + Sweet + Bitter + Salt +

Speech.—No dysarthria, dyspraxia or aphasia. Motor—abnormal muscular movements—intermittent convulsions right eyelids and right sternocleido mastoid. Muscle strength—good except during and just after spells. Paralysis—none. Posture—normal. Tonus—seems normal. Coördination—gait normal. Kernig's R-O. L-O. Romberg absent. Diadochokinesia normal. Finger finger fair—equal. Finger nose fair—equal. Figures with feet fair. Trophic—no atrophy. Reflexes—deep. Right—Biceps + Triceps + Radial + Ulnar + Patel. + Achil. + Left—Biceps + Triceps + Radial + Ulnar + Patel. + Achil. +

Superficial Reflexes.—Right—Up.ab. + L.ab. + Plan. + Babin.0 Left.—Up.ab + L.ab. + Plan. + Babin.0 Clonus absent. Sensation—touch normal. Muscle sense good. Joint sense good. No pain. Stereognosis good. Secretion—excessive sweating in axillae. Vesical functions good control. Rectal functions good control. Fever 99°. Head—no injury. Face—adenoma sebaceum—symmetrically on nose, cheeks and chin. Eyes—no inflammation. Ears—no earache except for one night in right ear two years ago. Nose—no trouble—used to bleed often last spring. Mouth—breath bad occasionally. No ulcers. Herpes on right upper lip. Tongue not coated. Teeth—two upper incisors missing and other two unusually large. Glandular—postcervical glands enlarged. Tonsils enlarged moderately. Thyroid slightly enlarged. Integument—hair normal—no jaundice. No warts. Angiomata none. Erup-

tions—adenoma sebaceum. Few moles on lower abdomen. Lungs—negative. No cough, sputum, night sweats, blood, pain in chest, or dyspnea. Respiration 22 to minute. Heart negative. Pulse 22 to one-quarter minute. Blood-vessels normal. Blood-pressure 112-60. Pulse irregular. Abdomen—negative. No hernia. Liver slightly palpable. Spleen and kidneys not palpable. Stomach seems normal. No belching, pain, nausea, vomiting or heart-burn. Intestines—no flatulence, constipation, mucus, diarrhea, blood or piles. Genitalia—adherent clitoris. Urinary—no dysuria, hematuria. Diuria 4-5 times. No nocturia. Bones—joints, no trouble. Spine—no trouble.

Laboratory Examinations.—Blood—hemoglobin, 80 per cent.; red blood-cells, 4,720,000; white blood-cells, 6,000. Wassermann—negative. Urine—straw, slightly cloudy, sp.gr. 1.015, acidity 2 to 25 cubic centimeters. Albumin negative, sugar negative, indican 3. Microscopic: 6 pus-cells per 0.1 cubic millimeter—otherwise negative.

Stool Examinations.—November 15, 1926, showed presence of hookworm. December 21, 1926, showed presence of hookworm. January 20, 1927, negative. February 3, 1927, showed presence of hookworm. February 22, 1927, showed presence of one ova. March 23, 1927, showed presence of hookworm. May 11, 1927, showed presence of hookworm. July 20, 1927, showed presence of very few ova. August 15, 1927, showed presence of hookworm. December 30, 1927, showed very light infection. February 7, 1928, showed very few eggs present. April 23, 1928, showed presence of hookworm. July 19, 1928, negative. October 8, 1928, negative. September 10, 1929, negative. October 3, 1930, negative.

Blood Chemistry.—Sugar 105.0 milligrams per 100 cubic centimeters blood. N.P.N. 33.3 milligrams per 100 cubic centimeters blood. Urea N(est) 20.0 milligrams per 100 cubic centimeters blood. Creatinin 1.3 milligrams per 100 cubic centimeters blood. Chlorids 511.5 milligrams per 100 cubic centimeters blood.

Discussion.—She did not complain any more of headaches. There were no tumors manifested in any other part of the body. She ceased to have any spells under the use of luminal but they returned in March, 1929, when she had them on the 15th, 16th, 17th and 18th and another one in April, 1929, at which time she was put on two and one-half grains of luminal every night and since then has had no further attacks.

Clinical Papers on Diseases Caused by Bacteria

SPECIFIC TRANSMISSIBLE DISEASES OF MAN, AND THE AGENTS CAUSING THEM

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THE promulgation of the newer systems of nomenclature in the classification of the bacteria, protozoa and metazoa has given rise to some confusion in the minds of physicians and surgeons, since the nomenclature which they studied is not always given as a synonym.

It has been deemed helpful in clearing up the confusion to list the common infectious diseases with the present name of the causative organisms and some of the synonyms under which the organisms had been known since their discovery. It is also deemed helpful to include in the list those diseases which are now believed to be caused by filtrable viruses.

Abscess.—This condition is caused by different bacteria. The most frequent cause is *Staphylococcus aureus* (syn. *Staphylococcus pyogenes aureus* Rosenbach, 1884). Less commonly the closely related species *Staphylococcus albus* and *Staphylococcus citreus* are encountered. *Apical abscess* (dental) is generally caused by streptococci of the alpha or viridans group, as *Streptococcus mitior* Schottmüller, 1903, *Streptococcus salivarius* Andrewes and Horder, 1906, and allied species. *Cerebral abscess* may be caused by *Actinomyces asteroides* (syn. *Cladothrix asteroides* Eppinger, 1890; *Streptothrix eppingeri* Rossi-Doria, 1891), by streptococci, staphylococci and by pneumococci. *Liver abscess* has been found to be caused by *Proteus americanus* Pacheco, 1928. *Pelvic abscess* is sometimes caused by *Micrococcus reniformis* (syn. *Diplococcus reniformis* Cotel, 1900). *Rectal abscess* has been produced by *Eberthella pyogenes* (syn. *Bacillus pyogenes foetidus* Passet, 1885). *Vaginal ab-*

cess has been caused by *Bacteroides fundibuliformis* (syn. *Bacillus fundibuliformis* Halle, 1898).

Acne.—*Corynebacterium acne* (syn. *Bacillus acne* Gilchrist, 1900) is generally believed to cause this infection.

Actinomycosis.—Caused by *Actinomyces hominis* Boström, 1890.

Alastrim.—Caused by a filtrable virus which is closely related to that causing variola. The pustules contain staphylococci.

Amebiasis.—Infections caused by amebae. Amebic abscess is caused by *Entamoeba kartulisi* (syn. *Amoeba kartulisi* Doflein, 1901). Amebic dysentery is caused by *Entamoeba histolytica* (syn. *Amoeba histolytica* Schaudinn, 1903), by *Entamoeba nipponica*, by *Entamoeba tetragena* Hartmann, 1908, and by *Entamoeba tropicalis*. Amebic gingivitis is caused by *Entamoeba gingivalis* (syn. *Amoeba buccalis* Gros, 1849).

Ankylostomiasis.—Infestation with *Ankylostoma duodenale* (syn. *Strongylus quadridentatus* v. Siebold, 1851).

Anthrax.—Caused by *Bacillus anthracis* Koch, 1876.

Apthous Fever (foot and mouth disease).—Caused by a specific filtrable virus.

Appendicitis.—Generally the primary causative agent is *Streptococcus pyogenes* Rosenbach, 1884. Other organisms are also found as secondary invaders, as *Escherichia coli* (syn. *Bacterium coli commune* Escherich, 1886), and *Clostridium welchii* (syn. *Bacillus aerogenes capsulatus* Welch and Nuttall, 1892).

Arthritis.—In this infection several species of genus *Streptococcus* have been reported: *Streptococcus pyogenes* (see appendicitis), *Streptococcus mitior* Schottmüller, 1903, *Streptococcus faecalis* Andrewes and Horder, 1906, and *Streptococcus cardioarthritidis* Small, 1927. Gonorrheal arthritis is due to *Neisseria gonorrhoeae* syn. The gonococcus, Neisser, 1879; *Diplococcus gonorrhoeae* Bumm, 1885).

Ascariidosis.—Infestation with roundworms, *Ascaris lumbricoides* Linné, 1758.

Asthma (bronchial).—The organisms encountered most frequently are *Streptococcus pyogenes* and *Staphylococcus aureus*.

Balantidiasis.—Caused by intestinal parasites, as *Balantidium coli* (syn. *Paramoecium coli* Malmsten, 1859), and *Balantidium minutum* Schaudinn, 1899.

Bilharziosis (see *Schistosomiasis*).

Botulism.—This is a condition of food intoxication. Toxin is formed in food by *Clostridium botulinum* (syn. *Bacillus botulinus* van Ermengem, 1896).

Bronchitis.—The bacteria found most commonly are *Streptococcus pyogenes* and *Diplococcus pneumoniae* Weichselbaum, 1886 (syn. *Microbe septicémique du saliva* Pasteur, 1881; *Micrococcus pasteurii* Sternberg, 1881; Lancet-shaped *Micrococcus*, Talmon, 1883; *Pneumoniemikrococcus* Fränkel, 1886; *Streptococcus lanceolatus pasteurii* Gamaleia, 1888; *Bacterium pneumoniae* Migula, 1900).

Bronchopneumonia.—The bacteria encountered most commonly are several or all of the following: *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Diplomoccus pneumoniae*; and less commonly *Hemophilus influenzae* (syn. *Influenza bacillus* Pfeiffer, 1892), and *Klebsiella pneumoniae* (syn. *Pneumoniococcus* Friedlander, 1882; *Bacterium pneumonie crouposae* Zopf, 1885; *Bacillus pneumoniae* Flügge, 1886; and *Bacterium pneumoniae* Migula, 1900).

Carbuncle.—This lesion is caused by *Staphylococcus aureus*, less frequently by *Staphylococcus albus*. *Malignant carbuncle* is caused by *Bacillus anthracis* Koch, 1876.

Caries (dental).—*Lactobacillus necrodentalis* Goadby appears to be responsible for the first stage of dental caries, the solution of the lime salts in the enamel and dentine. In the eroded area other bacteria having proteolytic powers liquefy the dentine. Caries is, therefore, a mixed infection. Disturbances in body metabolism are fundamental to the bacterial attack on the teeth.

Catarrh.—*Neisseria catarrhalis* (syn. *Micrococcus catarrhalis* Pfeiffer, 1896) and *Staphylococcus pharyngis* Bergey et al., 1923, are commonly found in catarrhal inflammation of the upper respiratory tract. Less frequently *Klebsiella capsulatus* (syn. *Kapselbacillus* Pfeiffer, 1889; *Bacillus capsulatus* Sternberg, 1892; and *Bacterium capsulatus* Migula, 1900) may be encountered.

Cellulitis.—*Streptococcus pyogenes*, *Staphylococcus aureus*, and *Diplococcus pneumoniae* are the organisms generally encountered. *Pelvic cellulitis* has been found to be caused by *Micrococcus minimus* (syn. *Staphylococcus minimus* Gioella, 1907).

Cervicitis.—Caused by *Neisseria gonorrhoeae* (see gonorrhea).

Chancre (soft).—Caused by *Hemophilus ducreyi* (syn. *Streptobacillus* of soft chancre, Ducrey, 1889).

Chancre (hard).—*Treponema pallidum* (syn. *Spirochaeta pallida* Schaudinn and Hoffman, 1905) is the causative organism.

Cholecystitis.—The following bacteria are frequently encountered: *Streptococcus faecalis* Andrewes and Horder, 1906; *Eberthella typhi* (syn. *Bacillus* der abdominal Typhus, Eberth, 1880; Typhus bacillus Gaffky, 1884; *Bacillus typhosus* Zopf, 1885; *Bacillus typhi* Schröter, 1886; *Bacillus typhi abdominalis* Flügge, 1886; *Vibrio typhosus* Trevisan, 1889; *Eberthus typhosus* Castellani and Chalmers, 1919), and *Escherichia coli* (syn. *Bacterium coli commune* Escherich, 1886).

Cholera.—*Vibrio comma* is the causative organism in epidemic cholera (syn. *Komma bacillus* Koch, 1884; *Pacinia cholerae asiaticae* Trevisan, 1885; *Microspira comma* Schröter, 1886; *Spirillum cholerae asiaticae* Flügge, 1886).

Chorea.—Believed to be caused by a filtrable virus, though streptococci are also frequently encountered.

Colitis.—This condition is caused by one or more of several organisms, as *Escherichia coli*, *Shigella dysenteriae* (syn. *Bacillus dysenteriae* Shiga, 1898; *Bacillus shigae* Chester, 1901), and *Shigella paradysenteriae* (syn. *Bacillus dysenteriae* Flexner, 1900; *Bacillus dysenteriae* Hiss, 1900; *Bacillus dysenteriae* Strong, 1906; *Bacillus paradysenteriae* Collins, 1905; weakly toxic strains of dysentery bacilli, Sonne, 1914).

Conjunctivitis.—Acute conjunctivitis may be caused by different bacteria, as *Diplococcus pneumoniae*, *Neisseria gonorrhoeae*, *Hemophilus conjunctivitis* (common name, Koch-Weeks bacillus), *Hemophilus lacunatus* (common name, Morax-Axenfeld bacillus), and *Corynebacterium diphtheriae* (syn. *Bacillus diphtheriae* Klebs, 1883).

Croup (diphtheritic).—Caused by the diphtheria bacillus.

Cystitis.—This is commonly caused by *Escherichia coli* or other members of the "colon" group of bacteria, or members of genus *Salmonella*.

Dengue Fever.—Caused by a specific filtrable virus.

Diarrhea (summer).—This is caused by different bacteria. Those found most commonly are: *Escherichia coli*, *Eberthella typhi*,

Shigella dysenteriae, *Shigella paradysenteriae*, *Proteus vulgaris*, and *Salmonella enteritidis*.

Diphtheria.—Caused by *Corynebacterium diphtheriae* (syn. *Bacillus diphtheriae* Klebs, 1883).

Distomiasis.—Infestation by trematode worms, as *Cladorchis watsoni* (syn. *Amphistoma watsoni* Cunningham, 1904); *Clonorchis epidemicus* Baelz, 1883; *Clonorchis sinensis* Cobbold, 1875; *Dracocœlium lanceolatum* Stiles, 1896; *Fasciola hepatica* Linné, 1758; *Fasciolopsis buski* Lankester, 1857; *Gastrodiscus hominis* (syn. *Amphistoma hominis* Lewis and McConnel, 1876); *Heterophyes heterophyes* v. Siebold, 1852; *Opisthorchis felineus* Rivolta, 1885; *Opisthorchis noverca* Braun, 1903; and *Paragonimus westermani* (syn. *Distoma westermani* Kerbert, 1878; *Distoma pulmonale* Baelz, 1883).

Dysentery (amebic).—Caused by *Entamoeba histolytica*, *Entamoeba nipponica*, *Entamoeba tetragena*, and *Entamoeba tropicalis*.

Dysentery (bacillary).—Caused by *Shigella dysenteriae* and by *Shigella paradysenteriae*.

Ecthyma (gangrenous).—The organism generally encountered is *Pseudomonas aeruginosa* (syn. *Bacterium aeruginosum* Schröter, 1872; *Bacillus pyocyaneus* Gessard, 1882).

Empyema.—The organisms commonly found in empyema are *Streptococcus pyogenes* and *Diplococcus pneumoniae*.

Encephalitis.—Caused by a specific filtrable virus.

Endocarditis (acute).—This infection is caused by *Streptococcus pyogenes* and by *Diplococcus pneumoniae*.

Endocarditis (lenta).—Caused by the alpha or viridans group of Streptococci, as *Streptococcus mitior*, and related species.

Enteritis.—This condition is due to infection by members of genus *Salmonella*, of which *S. paratyphi*, *S. schottmülleri*, *S. enteritidis*, and *S. suipestifer*, are encountered most frequently.

Epithelioma Contagiosa.—Caused by a specific filtrable virus.

Epitheliosis Conjunctivae.—Caused by a specific filtrable virus.

Erysipelas.—Caused by *Streptococcus erysipelatis* Fehleisen, 1882.

Filariasis.—Infestation of blood and tissues by nematode worms, as *Acanthocheilomenia perstans* (syn. *Filaria perstans* Manson, 1891), *Filaria bancrofti* Cobbold, 1877 (syn. *Filaria sanguinis*

hominis Hall, 1885), *Filaria loa* Guyot, 1778 (syn. *Dracunculus loa* Cobbold, 1864), *Filaria medinensis* Linné, 1758 (syn. *Dracunculus medinensis* Cobbold, 1864) and *Filaria demarguayi* Manson, 1897.

Food Poisoning.—Produced by *Clostridium botulinum*, by *Salmonella enteritidis* and related species, or by *Proteus vulgaris*.

Furuncle.—Caused by *Staphylococcus aureus* and *Staphylococcus albus*.

Gangrene (appendix).—*Bacteroides fragilis* (syn. *Bacillus fragilis* Veillon and Zuber, 1898) and *Clostridium welchii* are often present, besides the primary cause of the inflammation.

Gangrene (hospital).—Anaërobic spore-forming bacteria and members of genus *Proteus* are encountered.

Gangrene (lung).—Vincent's infection due to *Fusiformis dentium* Hoelling, 1889, and *Borrelia vincenti* Vincent, 1896, are generally found.

Gas Gangrene of Wounds.—Anaërobic spore-forming bacteria are responsible for this condition. *Clostridium welchii* occurs most frequently.

Giardiasis.—Caused by a flagellate parasite, *Giardia lamblia* (Stiles) Kofoid, 1915.

Glanders (farcy).—Caused by *Pfeifferella mallei* (syn. *Rotzbacillus*, Löffler, 1886).

Gonorrhea.—Caused by *Neisseria gonorrhoeae* (syn. *Diplococcus gonorrhoeae* Bumm, 1885; *Micrococcus gonorrhoeae* Flügge, 1886).

Granuloma.—Caused by *Klebsiella granulomatis* (syn. *Calymmatobacterium granulomatis* Beaurefaire-Aragao and Vianna, 1912):

Herpes Simplex.—Caused by a specific filtrable virus.

Herpes Zoster.—Caused by a specific filtrable virus.

Impetigo Contagiosa.—Caused by *Streptococcus pyogenes*.

Inflammation.—The most frequent causes are streptococci, staphylococci and pneumococci.

Influenza.—*Hemophilus influenzae* (syn. *Influenza bacillus* Pfeiffer, 1892) is commonly associated with the disease and is still believed by some to bear a causative relation. There is some evidence to believe that the disease is caused by a specific filtrable virus.

Jaundice (hemorrhagic).—Caused by *Leptospira icterohaemorrhagiae* (syn. *Spirochaeta icterohaemorrhagiae* Inada and Ido, 1916).

Kala-azar.—Infection by parasites as *Herpetomonas donovani* (syn. *Leishmania donovani*) and *Herpetomonas infantum*.

Laryngitis.—Streptococci and pneumococci are found most frequently.

Leishmaniasis.—Infection by *Herpetomonas donovani*, *Herpetomonas infantum*, in Kala-azar, and *Herpetomonas tropica*, in tropical sore.

Leprosy.—Caused by *Mycobacterium leprae* (syn. *Bacillus leprae* Hansen, 1879).

Lupus.—*Mycobacterium tuberculosis* (syn. *Bacillus tuberculosis* Koch, 1884) is the causative organism.

Lymphadenitis.—Caused by the tubercle bacillus, the plague bacillus, the Ducrey bacillus, or the gonococcus.

Lymphangitis.—Caused by *Streptococcus pyogenes*.

Malaria.—Infection by blood parasites, as *Plasmodium falciparum* (syn. *Laverania malariae* Grassi and Feletti, 1890), *Plasmodium malariae* Laveran, 1883, and *Plasmodium vivax* Grassi and Feletti, 1892.

Malignant Edema.—Caused by *Clostridium septicus* (syn. *Vibrio septique* Pasteur and Joubert, 1877, *Bacillus oedematis maligni* Koch, 1881).

Malta Fever.—Caused by *Brucella melitensis* (syn. *Micrococcus melitensis* Bruce, 1887, *Alcaligenes melitensis* Bergey *et al.*, 1923).

Mammitis.—Caused by *Staphylococcus aureus*.

Mastoiditis.—Caused by *Streptococcus pyogenes* and *Diplococcus pneumoniae*.

Measles.—Generally believed to be caused by a specific filtrable virus, though it appears possible that *Streptococcus morbilli* Ferry and Fisher, 1929, may have some relation to the etiology of the disease.

Melioidosis.—Attributed to *Flavobacterium pseudomallei* (syn. *Bacillus pseudomallei* Whitmore, 1913; *Bacillus whitmori* Stanton and Fletcher, 1925).

Meningitis (epidemic). Caused by *Neisseria intracellularis* (syn. *Diplococcus intracellularis meningitidis* Weichselbaum, 1887).

Meningitis (sporadic).—Caused by different bacteria of which the following occur most frequently: *Streptococcus pyogenes*, *Diplococcus pneumoniae*, *Staphylococcus aureus*, *Mycobacterium tuber-*

culosis, *Hemophilus influenzae*, and *Diplococcus mucosus* v. Lingelsheim, 1908.

Metritis.—Caused by different bacteria, as follows: *Streptococcus pyogenes*, *Streptococcus puerperalis*, *Streptococcus anhaemolyticus*, *Staphylococcus aureus*, and *Staphylococcus albus*.

Mumps.—Caused by a specific filtrable virus.

Mycetoma.—Caused by *Actinomyces madurae* (syn. *Streptothrix madurae* Vincent, 1894), and *Actinomyces freeri* (syn. *Streptothrix freeri* Musgrave and Clegg, 1907).

Mycosis Intestinalis.—Caused by *Bacillus anthracis* Koch, 1876.

Myocarditis.—Commonly due to *Streptococcus pyogenes*.

Neuritis.—Generally caused by species of genus *Streptococcus*.

Osteitis.—Caused by *Staphylococcus aureus* and by *Staphylococcus albus*.

Osteomyelitis (see osteitis).

Otitis.—Due to infection by *Diplococcus pneumoniae*, by *Streptococcus pyogenes*, and by *Staphylococcus aureus*.

Oxyuriasis.—Infestation with seatworms, *Oxyuris vermicularis* (Linné), 1767.

Ozena. The following bacteria may be encountered, *Klebsiella ozaenae* (syn. *Bacillus ozaenae* Abel, 1893), *Escherichia foetida* (syn. *Coccobacillus foetidus* of ozena, Perez, 1899) and *Pseudomonas smaragdina* (syn. *Bacillus smaragdinus foetidus* Reiman, 1900).

Pancreatitis.—Generally due to *Streptococcus pyogenes*.

Pappataci Fever (sand-fly fever).—Caused by a specific filtrable virus.

Paratyphoid Fever.—The following members of genus *Salmonella* are the most common causes of this disease: *Salmonella paratyphi* (syn. *Bacterium paratyphosum* Brion and Kayser, 1902), *Salmonella schottmülleri* (syn. *Bacillus paratyphi alcaligenes* Schottmüller, 1900), and *Salmonella aertricke* (syn. *Bacilus aertrycke* De Nobele, 1901). Other members of the genus are encountered less frequently.

Parrot Fever (Psittacosis).—This disease is now believed to be due to a specific filtrable virus, though formerly it was supposed to be caused by *Salmonella psittacosis* (syn. *Bacterium psittacosis* No-card, 1893).

Pericarditis.—*Streptococcus pyogenes* and *Diplococcus pneumoniae* are found as the most frequent causes of this disease.

Peritonitis.—Generally caused by *Streptococcus pyogenes* as the primary agent. Colon bacilli, fecal streptococci, and anaërobic spore-forming bacteria may occur as secondary invaders.

Pertussis.—Caused by *Hemophilus pertussis* (syn. Microbe de Coqueluche Bordet and Gengou, 1906).

Pharyngitis.—Caused by different types of streptococci and by pneumococci.

Phlebitis.—Caused by *Streptococcus pyogenes*.

Phthisis.—Caused by *Mycobacterium tuberculosis* (syn. *Bacillus tuberculosis* Koch, 1884).

Plague.—The disease bubonic plague is caused by *Pasteurella pestis* (syn. *Bacillus pestis* Yersin and Kitasato, 1894).

Pleuritis.—Caused by *Streptococcus pyogenes* and by *Diplococcus pneumoniae*.

Pneumonia.—The most frequent cause is *Diplococcus pneumoniae*. A small percentage of cases is due to *Klebsiella pneumoniae* (syn. *Pneumoniococcus* Friedlander, 1882; *Bacterium pneumoniae crouposae* Zopf, 1885; *Bacterium pneumoniae* Migula, 1900).

Poliomyelitis.—Caused by a specific filtrable virus.

Prostatitis.—Different bacteria are encountered in this disease, as *Neisseria gonorrhoeae*, *Streptococcus pyogenes*; streptococci of the alpha or viridans group, *Staphylococcus aureus*, *Corynebacterium pseudodiphtheriticum* (syn. *Bacillus pseudodiphtheriticus* Kruse, 1896; *Bacterium pseudodiphtheriticum* Migula, 1900; *Mycobacterium pseudodiphtheriticum* Chester, 1901).

Prowazekiasis.—Blood-stream infection by parasites, as *Prowazekia cruzi*, *Prowazekia parva*, and *Prowazekia weinbergi*.

Pseudoglanders (see melioidosis).

Psittacosis (see parrot fever).

Pyelonephritis.—The following bacteria are encountered most frequently: *Escherichia coli*, *Eberthella typhi*, and *Mycobacterium tuberculosis*.

Pyuria.—Caused by bacteria of the "colon" and the "paratyphoid" groups.

Rabies.—Caused by a specific filtrable virus.

Rat-Bite Fever.—Caused by *Leptospira icterohaemorrhagiae* (syn. *Spirillum minus* Carter, 1887; *Spirillum morsus muris* Futaki, 1915; *Spirochaeta icterohaemorrhagiae* Inada and Ido, 1916).

Relapsing Fever.—This disease is caused by a spiral organism which is found in the blood of the patient. The organisms found in this disease in different parts of the world vary somewhat from those found in other countries. There is also a difference in the insects which transmit the organisms. The organisms are *Borrelia recurrentis* (syn. *Spirillum* of relapsing fever, Obermeieri 1873; *Spirillum recurrentis* Lebert, 1874; *Spirillum obermeieri* Cohn, 1875), *Borrelia duttoni* (syn. *Spirochaeta duttoni* Breinl, 1907), *Borrelia carteri* (syn. *Spirillum carteri* Mackie, 1907), *Borrelia kochii* (syn. *Spirochaeta kochii* Shellack, 1907), *Borrelia berbera* (syn. *Spirochaeta berbera* Sargent and Foley, 1908), *Borrelia novyi* (syn. *Spirochaeta novyi* Shellack, 1907), and *Borrelia egyptica* (syn. *Spironema egyptica* Balfour, 1910).

Rheumatic Fever.—Streptococci have been suspected of causing this disease. Cecil and his associates found the alpha or viridans group of streptococci of the type of *Streptococcus faecalis* Andrewes and Horder, 1906. *Streptococcus cardioarthritidis* Small, 1927, is also still under investigation. Recently Clawson has made a claim for a streptococcus of the alpha or viridans group as the cause of the disease. There is some reason to believe that the disease is due to a filtrable virus.

Rhinitis (acute).—This infection is generally caused by streptococci, staphylococci, or pneumococci.

Rhinitis (chronic).—In this infection *Escherichia foetida* is generally found.

Rhinitis (membranous).—This disease is caused by *Corynebacterium diphtheriae*.

Rhinoscleroma.—Caused by *Klebsiella rhinoscleromatis* (syn. *Rhinoscleroma bacillus* v. Fritsch, 1882).

Rocky Mountain Fever.—A disease transmitted by the bite of ticks. Rickettsia bodies have been found in the blood and internal organs of patients.

Salpingitis.—Caused by *Neisseria gonorrhoeae*.

Sarcosporidiosis.—Infection by muscle parasites, *Sarcocystis*

lindemanni (syn. *Gregarina lindemanni* Rivolta, 1878) and *Sarcocystis hominis* Rosenberg, 1892.

Scarlet Fever.—Many investigators believe this disease is caused by a specific filtrable virus, though *Streptococcus scarlatinae* Klein, 1886, is closely associated if it is not the actual cause.

Schistosomiasis.—Infestation with *Schistosoma haematobium* (syn. *Distoma haematobium* Bilharz, 1852), *Schistosoma japonica* Katsurada, 1904, and *Schistosoma mansoni* Sambon, 1907.

Septic Sore Throat.—Caused by *Streptococcus epidemicus* Davis, 1912.

Septicemia.—This type of infection is caused by *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Diplococcus pneumoniae*. *Puerperal septicemia* is generally caused by *Streptococcus puerperalis* Arloing, 1882.

Sinusitis.—The following bacteria are found most frequently: *Streptococcus pyogenes*, *Diplococcus pneumoniae*, *Klebsiella pneumoniae*, and *Hemophilus influenzae*.

Sleeping Sickness (African).—Caused by *Trypanosoma gambiense* Dutton, 1907, and *Trypanosoma rhodesiense* Stephens and Fantham.

Sore (tropical).—Caused by *Herpetomonas tropica* (syn. *Leishmania tropica*).

Sore Throat.—The following bacteria are encountered: *Streptococcus pyogenes*, *Streptococcus anginosus* Andrewes and Horder, 1906, *Streptococcus ignavus* Holman, 1916, and *Micrococcus syzygios* (syn. *Micrococcus syzygios scarlatinae* Herzberg, 1929).

Stomatitis.—The organisms of Vincent's infection and *Oidium lactis* are found.

Strongylosis.—Infestation with *Strongylus stercoralis*.

Suppuration.—Staphylococci, streptococci, pneumococci, gonococci, and meningococci are the common causes of pus formation.

Syphilis.—*Treponema pallidum* is the cause of this disease.

Tabes.—Caused by *Treponema pallidum*.

Taeniasis.—The following tapeworms are encountered in man: *Davainea madagascariensis* (syn. *Taenia madagascariensis* Davaine, 1869), *Diphyllobotrium cordatus* Lüke (syn. *Bothriocephalus cordatus* Leuckhart, 1863), *Diphyllobotrium latum* (syn. *Taenia lata* Linné, 1748), *Diphyllobotrium mansoni* (syn. *Bothriocephalus man-*

soni Cobbold, 1883), *Diplogonosporus grandis* Blanchard, 1894, *Hymenolepis lanceolata* (syn. *Taenia lanceolata* Block, 1782), *Hymenolepis nana* (syn. *Taenia nana* v. Siebold, 1852), *Taenia africana* Linstow, 1900, *Taenia saginata* Goeze, 1782 (syn. *Taenia mediocanellata* Kűchmeister, 1855), and *Taenia solium* Linné, 1767.

Tetanus.—Caused by *Clostridium tetani* (syn. *Bacillus tetani* Nicolaier, 1884).

Thyroiditis.—Caused by *Streptococcus pyogenes*.

Tonsillitis.—The most frequent cause is a species of genus *Streptococcus*.

Trachoma.—Believed to be caused by a specific filtrable virus, though *Bacterium granulosis* Noguchi, 1928, is believed to bear some relation to the infection.

Trench Fever.—Caused by a specific filtrable virus.

Trichinosis.—Infestation with *Trichinella spiralis* (syn. *Trichina spiralis* Owen, 1835).

Trichiuriasis.—Infestation with *Trichiuris Trichiura* (syn. *Trichocephalus trichiuris* Linné, 1771).

Trichomoniasis.—Flagellate parasites invading the intestinal tract, as *Trichomonas hominis* and *Trichomonas minuta*, and the vagina, as *Trichomonas vaginalis*.

Trichostrongylosis.—Infestation with *Trichostrongylus instabilis*.

Trypanosomiasis.—Flagellate parasites infecting the bloodstream and central nervous system, as *Trypanosoma gambiense* Dutton, 1907, and *Trypanosoma rhodesiensis* Stephens and Fantham.

Tsutsugamushi Disease.—Caused by a specific virus.

Tuberculosis.—Caused by the human, bovine and avian types of the tubercle bacillus.

Tularemia.—Caused by *Pasteurella tularensis* (syn. *Bacterium tularense* McCoy and Chapin, 1910).

Typhoid Fever.—Caused by *Eberthella typhi* (syn. *Bacillus der abdominal typhus*, Eberth, 1880; *Bacillus typhi* Schröter, 1886).

Typhus Fever.—Caused by a specific virus.

Ulcer.—Staphylococci, streptococci, *Proteus vulgaris* and *Pseudomonas aeruginosa* are commonly found. *Duodenal* and *gastric* ulcers are caused by streptococci. *Phagedenic* ulcers are caused by *Borrelia phagedenis* (syn. *Spirochaeta phagedenis* Noguchi, 1912).

Uncinariasis.—Infestation with *Necator americanus* (syn. *Uncinaria americana* Stiles, 1902).

Undulant Fever.—Caused by *Brucella abortus* (syn. *Bacterium abortus* Bang, 1897).

Vaccinia.—Caused by the modified (attenuated) virus of variola.

Vaginitis.—Caused by *Neisseria gonorrhoeae*.

Varicella.—Caused by a specific filtrable virus.

Variola.—Caused by a specific filtrable virus, though the pustules contain *Streptococcus pyogenes*.

Vincent's Angina.—Caused by *Fusiformis dentium* and *Borrelia vincenti*.

Vulvitis.—Caused by *Neisseria gonorrhoeae*.

Whooping Cough (see pertussis).

Yaws.—Caused by *Treponema pertenue* Castellani, 1905.

Yellow Fever.—Believed to be caused by a specific filtrable virus. The disease was at one time believed to be caused by *Salmonella icteroides* (syn. *Bacillus icteroides* Sanarelli, 1897), and later by *Leptospira icteroides* Noguchi, 1919.

The infections caused by fungi have not been included in the foregoing list.

RAT-BITE FEVER IN THE UNITED STATES*

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THE geographic and historic pathology of rat-bite fever indicates that a peculiar disease of man, following the bite of a rat, has been recognizable for many years among many peoples in many different parts of the world. If Row⁴⁷ is correct in his interpretation of the writings of Wagabhatt, a physician of the fourth century B.C., rat-bite fever has been known in India for 2300 years. India may have been its source. In more recent times, the modern medical literature on the disease began with the paper by Wilcox⁶⁸ in 1840. During the ninety years since then, case reports have been published by physicians in nearly all the countries of the world. Ruge,⁴⁹ in a recent review, collected 329 of these reports, describing cases in continental Asia, Japan, Hawaii, Australia, the islands of the Pacific Ocean, Europe, England and in North and South America. It is apparent, therefore, that the disease has gained a world-wide distribution.

One extraordinary aspect of this world-wide distribution is that there has never been an epidemic spread of the special organism which causes the disease. The spread has been almost entirely through the agency of wild rats (*Mus decumanus etc.*). Several cases have been attributed to the bites of cats, weasels, pigs and other animals. While a few of these animals may be infected, the chief reservoir is in rats. The incidence of the infection in rats must vary greatly in different places. Surveys of rats in Japan, recorded by Kusama³⁰ and his associates, showed that from 6 to 13 per cent. of the rats were infected. Ruys⁵⁰ found the infection in 1 per cent. of the rats examined in Amsterdam, while Joekes²⁰ found an incidence of 25 per cent. of infection in rats in London. No rats were found to be infected among seventy-three examined by Leadingham³³

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in Georgia and among twenty-five examined by me⁶ in Rochester, New York. It seems likely, therefore, that the general level of infection of rats is low. There is no evidence that the flea or any other insect is concerned in the transmission of the disease and simple contact between infected animals or human beings does not spread it. The disease is primarily a wound infection—a mode of dissemination which accounts for the sporadic occurrence of the cases. Since no one has found the infecting organism on the teeth and only occasionally in the mouths of rats, the means by which it enters the wound made by the bite remains mysterious. Some writers have suggested that the organism, in the blood of the rat, gets into the wound from the abraded gums of the biting animal. It seems unlikely, however, that a rat injures its gums sufficiently to cause bleeding when it bites the flesh of babies or even the calloused hands of some of the hardy men who have suffered with this malady. Mooser³⁰ noticed that rats, whose bites were infective, had interstitial keratitis and conjunctivitis, with organisms in the exudate. He suggested that the organism passed down the lacrimal duct into the nose and on the lip or into the pharynx, and thence into the mouth and on the teeth of the rat. From these locations the organisms might get into the wounds made by the teeth. It is certain that there are very few organisms in the mouths of infected rats. In some experiments, only the first guinea pig bitten by a rat was infected while other animals subsequently bitten by the same rat were not infected. On the other hand, some of the cases to be reviewed in this paper give several instances of two individuals contracting the disease from the consecutive biting of the same rat (Cases: 7 and 8, 26 and 27, 35 and 36, Table I). From this consideration of the rat in relation to the distribution of the disease, it is apparent that living conditions and occupations which place man in close association with rats and the season of the year in which rats are most numerous are apt to be the most important influences controlling the incidence of rat-bite fever.

Another curious feature of the distribution of rat-bite fever is the existence of large areas apparently free from infection in the midst of infected territory. Cuba and the American tropics form one of these areas. Cases have been reported from Mexico, but none has been recorded in Cuba. I have been informed that physicians in

the widely extended medical service of the United Fruit Company have not seen any cases of this disease in any of the tropical countries in which the plantations of that company are situated. In the United States there are other areas of apparent freedom from this infection. This condition may be an artificial one, due to unrecorded observations on cases which have been seen or to my failure to find the reports in my search of the literature. I shall be glad to receive these reports. Perhaps, calling attention to the apparently exempt zones, which is one of the purposes of this article on the occurrence of rat-bite fever in the United States, will elicit additional reports and further etiologic investigations.

In the American medical literature of the past ninety years, I have found records of eighty-one cases of this disease in man following the bite of a rat, and a few other animals. None of these cases was rabies, which, of course, would be recorded in another category. In an attempt to sort out the cases of true rat-bite fever in the older clinical records, and from some of the recent diagnoses, unsupported by bacteriologic investigations, I have been guided by the well-established clinical criteria of the typical disease. Since comprehensive description of the disease and its modifications have been published by Miyake,³⁵ Proescher,⁴² Crohn,¹¹ Ruge,⁴⁰ Robertson⁴⁵ and others, it is not necessary to repeat the detailed symptomatology. The essential features are: The bite of a rat (or other animal in rare instances), which usually heals in a few days. In view of the possibility of the implantation of various pyogenic micro-organisms into the wound made by the teeth, it is remarkable how often this wound heals promptly. Nevertheless, in some cases a pyogenic process, due to streptococci, staphylococci and probably to the streptothrices described by Schottmüller,⁵² Blake⁷ and Tunnickliff^{60, 61} starts at once. In other cases, if this pyogenic infection does not come from the rat it is superimposed by surgical treatment or by the poulticing of the bite with bacteria-laden substances. Pyogenic infections of this nature have obscured many of the cases of rat-bite fever. They have been the only pathologic process in other cases of supposed rat-bite fever. Clinical reports of obvious pyogenic infection following the bites of rats should be excluded from the records under consideration. On this basis, I shall suggest the omission of some of the reported cases from the series listed below and indicate a doubt as to

the validity of others. After an incubation period of one to three weeks, the area bitten becomes swollen, painful, purplish red and develops a chancre-like ulcer. There is no pus in this primary induration. At this time there is generally a regional lymphangitis and lymphadenitis, accompanied by malaise, muscular pains, headache, slight chills and fever. A skin rash may appear at this time or may not appear until some days or weeks later. The eruption often appears first in the region of the body adjacent to the rat bite. It consists in bluish red or purple raised areas, starting as small points of reaction and later becoming a large blotchy maculo-papular rash on the skin of the arms, body, legs and sometimes the face. The intensity of the rash increases and decreases with the paroxysms of fever. The patient has periodic febrile periods, the temperature rising abruptly to 101° to 105° F., remaining elevated for two or three days and then returning to normal. After an interval of four to six days the temperature rises again and this cycle may be repeated frequently. There is generally a leukocytosis, with a white blood count of 10,000 to 14,000, and an increase in the polymorphonuclear neutrophils to 70 or 80 per cent. The leukocyte count has been observed to rise and fall with the paroxysms of fever. If the disease continues for weeks or months, the primary lesion may heal slowly or may become gangrenous. The skin eruption may increase in extent and severity, leaving coppery-colored areas or exfoliating swellings at the sites of old lesions. Alopecia may occur. The patient becomes weak and emaciated and has a moderate or severe degree of secondary anemia. Muscular atrophies have been seen in long-standing cases. There are no records of the formation of gummata.

A tabulated summary with a critical estimate of eighty-one cases diagnosed as rat-bite fever reported in American medical journals during the period 1839 to 1930 is presented, in Table I.

In compiling the list of cases summarized in Table I, I have omitted several referred to by other writers and have added a number which were not included in any previous collection. Some of the cases included in the lists which have been passed from article to article did not occur in the United States, some were obvious duplicate reports, and others were not cases of rat-bite fever. After a review of all the available case-histories, it seems that those numbered 4, 5, 10, 11, 44 and 50 might be omitted on the ground that

TABLE I

Rat-Bite Fever in the United States

List of Cases Reported, 1839-1930

Case No.	Author	Year	State	Sex	Age	Specific Treatment	Result	Animal	Remarks
1	Wilcox (66)	1839	Louisiana	M	40	None	Recovered ?	Rat	Typical. 1st case reported in U.S.A
2	Watson (63)	1840	New York	M	55	"	Recovered	"	Typical. Data scanty
3	Reece (43)	1866	Illinois	M	38	"	"	"	Typical
4	"	1866-72	"	?	?	"	?	Pig	Doubtful. Pyogenic infection
5	"	"	"	?	?	"	?	Squirrel	Doubtful. Pyogenic infection
6	"	"	"	?	?	"	?	Rat	Probable
7	Gilliam (24)	1868	Ohio	F	25?	"	Recovered	"	Typical
8	"	1868	"	F	Child	"	"	"	Typical
9	"	1869	"	F	"	"	Died	"	Probable
10	"	1869	"	F	"	"	"	"	Doubtful. Pyogenic infection
11	"	1869	"	F	"	"	"	"	Doubtful. Pyogenic infection
12	Farquhar (18)	Before 1869	"	?	?	"	"	"	Probable. Gangrene
13	"	"	"	?	?	"	Recovered	"	Probable. Data scanty
14	"	"	"	?	?	"	"	"	Probable. Data scanty
15	"	"	"	?	?	"	"	"	Probable. Data scanty
16	"	"	"	?	?	"	"	"	Probable. Data scanty
17	"	"	"	?	?	"	"	"	Probable. Data scanty
18	Packard (39)	1871	Pennsylvania	M	7	"	"	"	Typical
19	Earle (15)	1871	Illinois	M	40	"	"	"	Typical

TABLE I (Continued)

Rat-Bite Fever in the United States

List of Cases Reported, 1839-1930

Case No.	Author	Year	State	Sex	Age	Specific Treatment	Result	Animal	Remarks
20	Banker (5)	1873	Pennsylvania	F	35	None	Recovered	Rat	Typical
21	"	1875	"	F	70	"	Death 6 mos.	"	Probable
22	"	1879	"	M	60	"	Death 9 mos.	"	Typical
23	"	1880	"	M	36	"	Death 1 mo.	"	Typical with tetanus
24	"	Before 1886	"	M	?	"	Recovered	"	Typical
25	Cook (10)	1885	Indiana	M	11	"	"	"	Typical
26	Evans (17)	1900	Mississippi	M	12	"	"	"	Typical
27	"	"	"	M	9	"	"	"	Typical
28	"	1902	Illinois	M	8	"	"	"	Typical
29	Proescher (42)	1909	Pennsylvania	M	7	Arsenacetin	"	"	Typical
30	Crohn (11)	1910	New York	M	15	None	"	"	Typical
31	Blake (7)	1915	Massachusetts	F	67	"	Died	"	Atypical. WaR. neg. Streptothrix infection. Endocarditis
32	Tileston (59)	1915	Connecticut	F	46	Salvarsan	Recovered	"	Typical. Streptothrix isolated
33	"	1915	"	M	32	"	"	"	Typical. Abortive
34	Littler (34)	1916	Tennessee	M	14	None	"	"	Typical. Streptothrix found
35	Gundrum (25)	1916	California	M	14 mos.	Cacodylate	" 4 mos.	"	Typical
36	"	1916	"	F	25?	None	Recovered	"	Typical. Abortive
37	O'Leary (38)	1917	Iowa	F	4	Arsphenamine	"	"	Typical. WaR. neg.
38	Brennemann (8)	1917	Illinois	M	10	Salvarsan	"	Weasel	Typical. WaR. pos. Probably syphilitic

TABLE I (Continued)

Rat-Bite Fever in the United States

List of Cases Reported, 1839-1930

Case No.	Author	Year	State	Sex	Age	Specific Treatment	Result	Animal	Remarks
39	Tunncliffe and Mayer (61)	1918	Illinois	F	13	None	Died	Rat	Typical. Streptothrix isolated. WaR. neg.
40	Post (41)	1919	W. Virginia	?	?	?	Recovered	"	Typical. Data scanty
41	"	1919	"	?	?	?	"	"	Typical. Data scanty
42	"	1919	"	?	?	?	"	"	Typical. Data scanty
43	Arkin (2, 3)	1919	W. Virginia	M	9	Neosarsphenamine	Recovered	Rat	Typical. WaR. neg.
44	Sanders (51)	1920	Oklahoma	M	3 mos.	None	Died	"	Doubtful. Pyogenic infection
45	O'Leary (38)	1921	N. Dakota	F	5	Arsphenamine	Recovered	"	Typical. WaR. neg.
46	Emmert (16)	1922	Iowa	M	10	Neosalvarsan	"	"	Typical. WaR. 2+ Father syphilitic
47	Reuben and Steffen (44)	1922	New York	F	2	"	"	"	Typical
48	"	1922	" "	F	23 wks.	Sulpharsphenamine	"	"	Typical
49	"	1923	" "	F	6	"	"	"	Typical
50	Rodgers (40)	1923	Pennsylvania	F	17 mos.	None	"	White Rat	Doubtful. Exanthem.
51	Shattuck and Theller (53)	1923	Massachusetts	F	3½ mos.	"	Recovered?	Rat	Typical. First etiologically proved case in U.S.A. WaR. neg.
52	Wegner (65)	1923	Nebraska	M	3	Neosalvarsan	Recovered	"	Typical
53	DeFronzo (12)	1923	New Jersey	F	2	"	"	"	Typical
54	Strauch and Bissell (55)	1923	Illinois	M	1	None	"	"	Typical. WaR. neg.
55	Foley (19)	1923	Iowa	M	10	Neosalvarsan	"	"	Typical

TABLE I (Continued)
Rat-Bite Fever in the United States
 List of Cases Reported, 1839-1930

Case No.	Author	Year	State	Sex	Age	Specific Treatment	Result	Animal	Remarks
56	Dembo, Ruh, Fargo, Taylor (13)	1924	Ohio	F	7 mos.	Sulpharsphenamine	Recovered	Rat	Typical. Sp. morbus muris, seen in serum from lesion. War neg.
57	Lanford (31, 32)	1924	Louisiana	?	?	Salvarsan	"	"	Typical. Second etiologically proved case in U. S.A.
58	Chassagnac (9)	1924	"	?	?	None	"	"	Probable. Data scanty
59	Ward (62)	1924	N. Carolina	M	3½	Sulpharsphenamine	"	"	Typical. Sp. morbus muris found in fluid from lymph node.
60	Baker (4)	1924	Indiana	F	10 mos.	Arsphenamine	"	"	Typical. War neg.
61	"	1924	"	M	12	Sulfarsenol	"	"	Typical. War neg.
62	"	1924	"	M	5	Arsphenamine	"	"	Typical. War neg.
63	Zahoraky (67)	1925	Missouri	?	?	Sulpharsphenamine	Recovered	Rat	Typical. Sp. morbus muris found in serum from lesion.
64	Hennerich (27)	1925	"	M	27	Salvarsan	"	"	Typical. War neg.
65	Leadingham (33)	1925-26	Georgia	?	?	Arsphenamine	"	"	Scanty data. Said to have been typical. Sp. morbus muris obtained from 2 of these cases.
66	"	"	"	?	?	"	"	"	
67	"	"	"	?	?	"	"	"	
68	Foster (21)	1926	Pennsylvania	F	14 mos.	"	"	"	Typical. War neg.
69	Bayne-Jones (6)	"	New York	M	48	"	"	"	Typical. War pos. Probable syphilis
70	Rubino (48)	1927	Louisiana	M	42	Neosalvarsan	"	"	Typical. War neg.
71	"	"	"	M	15?	"	"	"	Typical

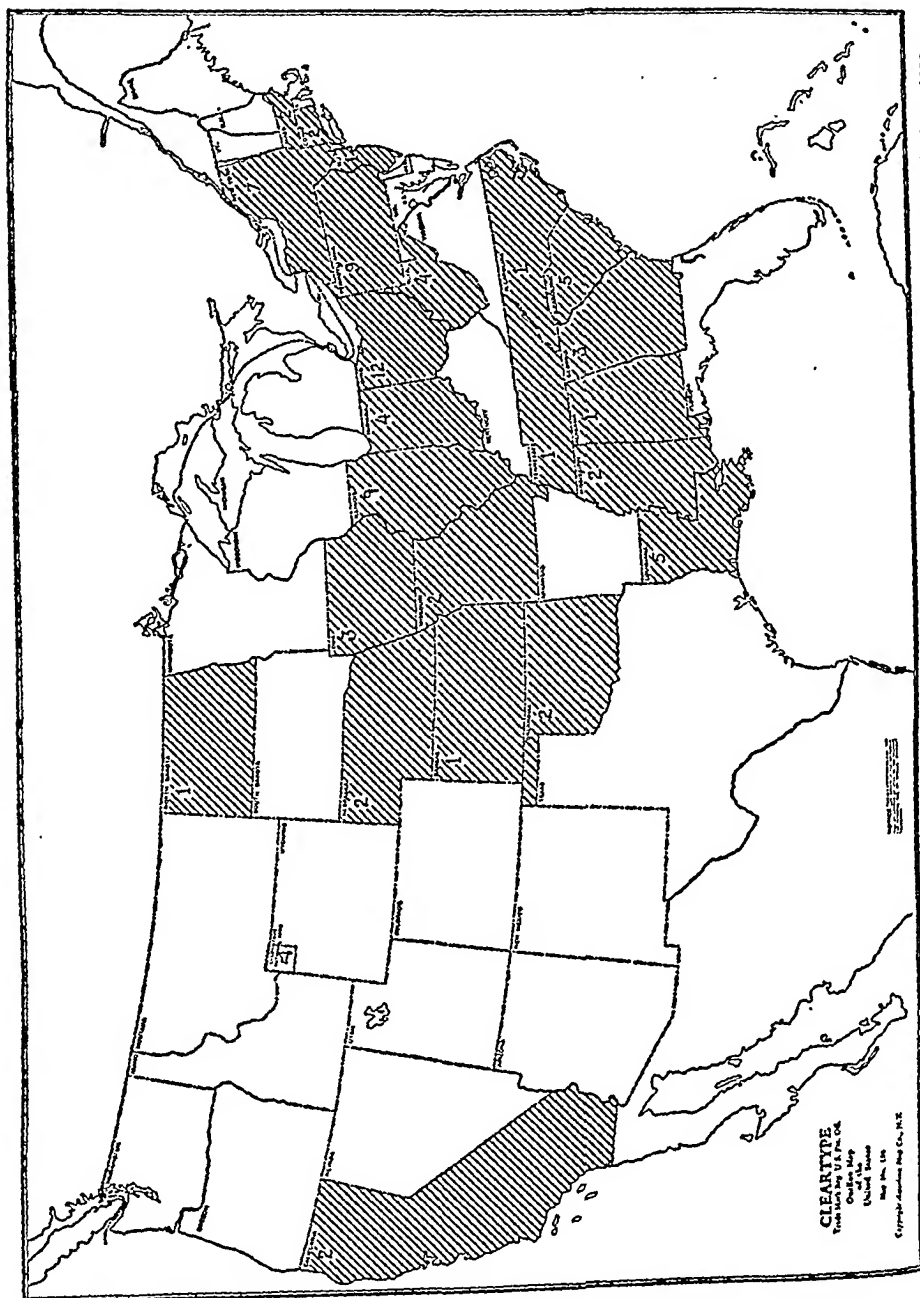
TABLE I (Continued)
Rat-Bite Fever in the United States
 List of Cases Reported, 1839-1930

Case No.	Author	Year	State	Sex	Age	Specific Treatment	Result	Animal	Remarks
72	Watson (64)	1927	Alabama	M	9	Neocarsphenamine	Recovered	Rat	Typical
73	Pine (40)	1928	Oklahoma	F	10	"	"	"	Typical
74	Dickinson (14)	"	New York	M	307	Arsphenamine	"	"	Typical. WaR neg.
75	Neel (37)	"	S. Carolina	M	6	Arsenical	"	"	Typical. WaR neg.
76	"	1929	"	?	?	"	"	"	Cases 75-79 said to have been typical.
77	"	"	"	?	?	"	"	"	Data scanty
78	"	"	"	?	?	"	"	"	
79	"	"	"	?	?	"	"	"	
80	Swab (57)	"	Nebraska	M	6	Neosalvarsan	"	"	Typical
81	Fontannon (20)	1930	Kansas	M	22	"	"	White rat	Typical. Protracted course. <i>Sp. morsus muris</i> said to have been isolated in blood culture.

they were not cases of rat-bite fever. This leaves a total of seventy-five cases recorded in the United States. The omission of these six cases has a distinct bearing upon an estimate of the fatality of the disease. Otherwise this omission is unimportant as it does not remove all the reports of the infection from any area.

The distribution among the States of disease following the bites of rats, and the few other animals mentioned, is shown graphically on the accompanying map (Fig. 1). From Table I and this map it is seen that rat-bite fever has been observed in twenty-three States. Table II presents the list of these States and the numbers of the cases of rat-bite fever occurring in them. The peculiar distribution of the disease in the United States appears clearly on the map. Delaware, Maryland, Virginia, Kentucky and Arkansas form a lane of apparently uninfected States between infected areas. All of the far-western States except California are apparently free from infection.

FIG. 1.



I have not found any reports of cases from Maine, Vermont, and New Hampshire. The explanation of the apparent freedom from infection existing in some States is not provided by the records of a general knowledge of rat populations and human living conditions. It is hoped that a search for rat-bite fever will be made in these States to establish the actual distribution of the disease.

TABLE II

Distribution of Total Cases (81) of Rat-Bite Fever by States

(This table includes six doubtful cases)

State	Case Numbers	Total
1. Alabama	72	1
2. California	35, 36	2
3. Connecticut	32, 33	2
4. Georgia	65, 66, 67	3
5. Illinois	3, 4, 5, 6, 19, 28, 38, 39, 54	9
6. Indiana	25, 60, 61, 62	4
7. Iowa	37, 46, 54	3
8. Kansas	81	1
9. Louisiana	1, 57, 58, 70, 71	5
10. Massachusetts	31, 51	2
11. Mississippi	26, 27	2
12. Missouri	63, 64	2
13. Nebraska	52, 80	2
14. New Jersey	53	1
15. New York	2, 30, 47, 48, 49, 69, 74	7
16. North Carolina	59	1
17. North Dakota	45	1
18. Ohio	7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 56	12
19. Oklahoma	44, 73	2
20. Pennsylvania	18, 20, 21, 22, 23, 24, 29, 50, 68	9
21. South Carolina	75, 76, 77, 78, 79	5
22. Tennessee	34	1
23. West Virginia	40, 41, 42, 43	4
		Total 81

It has often been said that the Wassermann reaction is positive in rat-bite fever. The data in Table I shed a good deal of light on this question. The results of this test were recorded in eighteen cases. Of these, fifteen were negative and three were positive. In each of these three cases, there was the possibility of a coincident syphilis.

In case 38, the patient's mother had a positive Wassermann reaction and a history of five miscarriages; in case 46, the patient's father was syphilitic, and this reaction should have been recorded doubtful as the serum was anticomplementary; in case 69, there was the possibility that the patient had latent syphilis. In general, the experience of foreign observers seems to be in accord with this. In addition, I have never found a positive Wassermann reaction to occur with the blood-serum of experimentally infected guinea pigs. It seems to me, therefore, that a negative Wassermann reaction is the rule in rat-bite fever, and that a positive reaction, if it is not a false positive result, indicates the possible existence of syphilis in the patient. Chaissaignac's case (No. 58) seems to have been one of superinfection with rat-bite fever upon an older syphilis. The data given by him, however, is inadequate to serve as a basis for a definite opinion on this phase of superinfection.

The mortality rate in rat-bite fever has been estimated to be about 10 per cent. It is true that in some series of reported cases, 10 per cent. of the patients have died from the effects of pyogenic infection, gangrene, bronchopneumonia and renal disease. But since there are many unrecorded cases of rat-bite fever and erroneously diagnosed cases, the available statistics on the deaths from this disease are obviously no true index of its fatality. In the series of eighty-one cases listed in Table I, there were ten deaths, giving a mortality of 12.3 per cent. It is proper, however, to remove from the list of fatal cases those numbered 10, 11, 23, 31 and 44. Cases 10, 11 and 44 seem to have been pyogenic infections. In case 23, tetanus was the cause of death, and the patient whose case is numbered 31, died of a streptothrix septicemia with ulcerative endocarditis. Excluding these five cases from consideration in this connection reduces the estimate of mortality to 6.17 per cent. No patient, in this list, has died of true rat-bite fever in the United States since 1920. Most have been cured by injections of arsenicals of the salvarsan type; others have recovered spontaneously. Certainly, the true mortality from the untreated disease is very low. In 1912, Hata²⁶ introduced salvarsan therapy in rat-bite fever, concluding from the analogies between syphilis and this disease, that salvarsan should be an effective remedy. It has indeed proved to be so efficacious that it seems unlikely that anyone will die of rat-bite fever if treatment with this type of

arsenical compound can be administered. One or two doses of salvarsan, arsphenamine or similar substance are usually sufficient to bring about a cure.

The rarity of rat-bite fever confers a sort of novelty upon this ancient disease. Occurrences of it usually call forth case reports. But the published records have a curious periodicity, explicable probably by the shifting of medical interests and by the effect of attention called to the disease by some new discovery concerning it. At least, artificial influences of this sort seem to offer a more logical explanation of the periodic variation in the publication of case reports than the supposition of actual changes in the incidence of infection. From Table III, in which the number of reports are listed by decades, it is seen that almost half as many cases, thirty-seven, were reported during the years 1920 to 1929 as in the whole period of ninety years. During this decade the stimulating influence was undoubtedly the etiologic discoveries of the Japanese in 1916.

TABLE III

Number of Case-Reports in the United States by Decades

<i>Period</i>	<i>Number Reported</i>
1839-49	2
1850-59	0
1860-69	12
1870-79	8
1880-89	3
1890-99	0
1900-09	4
1910-19	14
1920-29	37
1930-	1
	—
Total	81

In 1916, Futaki, Takaki, Taniguchi and Osumi,^{22, 23} published the account of their discovery in the lesions of rat-bite fever in man of a spiral organism which they named *Spirochaeta morsus muris*. The disease could be reproduced in animals by injection of this organism, the organism was found in infective rats, and aside from obtaining cultures of the organism, all of Koch's postulates were fulfilled in experiments made with it. The findings of these investigators have been confirmed repeatedly and the disease has been reproduced in nearly all its forms in human beings inoculated with this

spirochete. In the United States, the organism has been seen in fluids or recovered by animal inoculation from five cases during the past six years. If search for it were made more frequently, it would undoubtedly be found more often. There are, however, difficulties in the way of "isolating" it from a patient. One of these is the mistaken effort, prompted by statements in text-books, to obtain the organism by means of ordinary cultures of blood or material from lesions. In my opinion, this spirochete has never been successfully cultivated. In a personal communication to me from Doctor Nagayo of the Imperial Institute for Infectious Disease at Tokyo, I have the admission that the Japanese investigators were in error when they supposed that they obtained growth of the spirochete in Shimamine's medium. Joekes²⁹ reported successful cultivation of the organism in a modified Vervoort's medium at one time, but has never been able to repeat the results. In collaboration with Miss Henrietta S. Rhees, I have attempted to cultivate the organism in many different media under many conditions and can only add a report of our failures to the similar accounts of others. It is also usually very difficult, if not possible, to find the organism by dark-field examination of the blood of a patient. It is sometimes found in serum expressed from the initial lesion or in material aspirated from an enlarged lymph node. The most certain procedures are to inject guinea pigs or white mice with five to ten cubic centimeters of blood, apportioned appropriately to the size of the animal, to inject into these animals material aspirated from lymph nodes or expressed from lesions, or to insert under the skin of the animal a piece of tissue excised from a lesion of the patient. If the spirochetes are present in any of these materials they will be discoverable by dark-field examination or in stained films of the blood of the infected guinea pig or white mouse about two weeks after the inoculation. More etiologic studies of this nature are needed with material from American cases, to establish the characteristics of the strain of spirochete causing the infection in this country and to make the diagnosis certain.

The organism is a relatively short spiral 2μ to 5μ in length. Somewhat longer forms may occur associated with short ones. The spiral curves have about one crest per micron and have a sharp pitch. Flagella can be seen at each end of some of the organisms in a well-lighted dark-field. I have never seen more than one flagellum at

each end of the "Rochester" and "Boston" strains of this organism. But tufts of flagella at each end have been described and photographed by Adachi,¹ Ruys,⁵⁰ Robertson,⁴⁵ and many others. The organism has an extraordinarily rapid, darting motility. The term "spirochete" has been used as if that were the accepted designation of the organism. There is, however, a great weight of authority, well expressed by Robertson,⁴⁵ in opposition to this view. Many investigators, regard the organism as a *spirillum*, related more closely to bacteria by its relative inflexibility and by its flagella. In these considerations there are involved difficult questions of taxonomy and nomenclature, which cannot be dealt with adequately here. Figures 2, 3 and 4 are photomicrographs showing the morphology of the organism and its size in comparison with leukocytes and erythrocytes. Since the organism resembles a *Treponema*, since it is sensitive to salvarsan, and since the disease it produces is a "model-infection" for studies of syphilis (Stühmer⁵⁰), it seems to me more natural to allow this organism to remain provisionally classified as a spirochete.

The disease may be said to require a generally acceptable name. While rat-bite fever is its most common designation, there is a tendency to use for it the Japanese term "Sodoku." This term would distinguish it from other febrile diseases following the bite of a rat. "Sodoku" as a name, however, possesses an exotic and artificial quality which seems to impede its use by English writers. In the English literature it is occurring most frequently in the reports on the experimental production of this infection in man for the thermic treatment of paresis.

In the United States the use of "Sodoku" in the treatment of general paralysis was begun by Solomon⁵⁴ and his associates in 1926 as a substitute for malarial therapy of this disease. Solomon and his collaborators infected twelve paretics with rat-bite fever. In 1929, Hershfield²⁸ and a group of collaborators treated seventy-two cases of general paralysis in this way, and in 1930, Teitelbaum⁵⁸ published a report of the use of "Sodoku" in fifteen cases of paresis. All of these have been preliminary reports. While they indicate that the febrile paroxysms of experimentally produced "Sodoku" may be of benefit to some cases of paresis, the final reports, to serve as a basis for estimation of its value, have not yet appeared. The availa-

bility of the organism when a strain is kept in guinea pigs, the ease of cure by salvarsan, the avoidance of the transfer of syphilitic blood and removal of the danger of transferring the more dangerous malignant tertian type of malarial parasite are obvious advantages in the use of this infection. It has, however, certain inconveniences and dangers. Inoculation of the spirochete into the skin or subcutaneous tissue of man produces a large and troublesome chancre-like lesion, and the skin eruption is temporarily disfiguring (Fig. 5). It is said that the destructive local lesion at the site of inoculation can be avoided by careful intravenous injection of the guinea-pig blood containing the spirochetes. In Hershfield's²⁸ group of cases, two deaths were attributed to the induced rat-bite fever. The results of the use of "Sodoku" in the treatment of paresis will be awaited with interest.

SUMMARY

A study of the distribution of rat-bite fever in the United States was made on the basis of case-reports in the American medical literature. Eighty-one cases have been diagnosed rat-bite fever in twenty-three States. Of these, seventy-five appear to have been genuine rat-bite fever, while six of the cases were probably pyogenic infection. A map of the distribution of the disease shows that large areas of the country are apparently free from the infection. It is suggested that a search for cases be made in these apparently exempt States.

The causative organism, called provisionally *Spirochaeta morsus muris*, has been found in at least five of the cases reported in this country. It appears to be identical with the organism discovered by Futaki and his associates in 1916 in rat-bite fever in Japan. It has not been cultivated in artificial media.

Various recent developments in the study of rat-bite fever (or "Sodoku") are reviewed briefly. The chief of these is the use of this infection for the thermic treatment of paresis.

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FIG. 2.



Spirochaeta morsus muris
(Boston strain) in blood of guinea-pig. Short form. Wright's stain. Photomicrograph. (x 1500.)

FIG. 3.



Spirochaeta morsus muris
(Boston strain) in blood of guinea-pig. Intermediate and long forms in same field. Wright's stain. Photomicrograph. (x 1500.)

FIG. 4.



Spirochaeta morsus muris
(Boston strain) in blood of guinea-pig. Short form for comparison with size of leukocyte. Forms of all these lengths may be found in blood of a guinea-pig at the same time. Wright's stain. Photomicrograph. (x 1500.)

FIG. 5.



Large chancre-like lesion on thigh of man inoculated intradermally with blood of guinea-pig containing *Spirochaeta morsus muris* (Rochester strain). This shows the lesion as it appeared twenty days after the inoculation. The macular rash, which was on the skin of the face, arms, and trunk is shown on the skin of the leg in this picture. This type of lesion is to be avoided if induced rat-bite fever is to be used for the thermic treatment of paresis.

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THE GENERAL PROBLEM OF RESPIRATORY DISEASES AS ILLUMINED BY COMPARATIVE DATA*

First Lecture

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IN A study of the phenomena of life of which disease forms a conspicuous part two activities enter, first, a general investigation or an observational study of a phenomenon as a whole, and second, an attempt to disentangle what we believe the factors that enter into it. In the field of pathology, experimentation and research are associated with the laboratory where the apparatus for disentangling and analyzing is assembled, while in practice, observation of the whole phenomenon is possible. Experimentation and observation cannot get on without one another and, indeed, they are, after all, alike except for the more advantageous position of one or the other for the study of certain aspects of the whole. Experiments are the milestones we plant along a rough and uneven road. They tell us whence we have come and whither we are going, but the road itself is the natural event with all its unknown factors. Faulty experimentation misleads by planting milestones off the road.

Disease as it commonly occurs is a highly individualized phenomenon. Among the infectious diseases, each individual attacked presents conditions slightly or markedly different from those of every other individual. To get at the linkage of phenomena leading to diversity rests with the physician. The laboratory experiments can give only general results supposed to underlie all cases. Practice examines series of individuals and often brings to light by comparative studies important features of disease which are then transferred to the experimental laboratory for coördination with other features. It would seem that practice deals more with individual variation, experimentation with underlying uniformity. As a result of this division of labor, the not infrequent conflict between the experimental

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and observational operations in the study of disease is partly due to the fact that the one group of observers may place too much emphasis on individual variations while the other may make too broad an application of experimental results. The conflict and interplay between the indoor and outdoor operations are, however, healthful and stimulating.

Variation, then, is what we observe when we begin the preliminary study of any disease in a broad way. The diseases particularly subject to variation are those of the mucous membranes, which are more or less easily accessible to a variety of insults, living and otherwise, from without. By diseases of the mucous membranes I mean those in which infectious agents multiply on the surface, in mucus and in serous secretions, in the gland recesses, or as parasites in the cellular elements forming the covering of these membranes. Such organisms are far more subject to modifying influences than are agents which live and multiply within organs or tissues where the environment is constant. The mucous membranes themselves are subject to wide physiologic variations in response to external changes. This variability is necessary for the maintenance of a constant environment of the internal organs.

If we go back to the early days of bacteriology when a rapid, almost explosive expansion of our knowledge of infectious agents followed the introduction of Koch's methods of culture, we find that the first successes were achieved in the study of the septic or blood diseases such as anthrax and certain induced diseases of animals. Here the conditions were relatively simple. The microorganisms appeared in the blood and tissues in pure culture. When certain diseases, in which the mucous membranes were the scene of multiplication and injury, were attacked, the problem became more difficult. The parasitic forms present in recesses and glands of the mucosa and multiplying in excess secretions preceded, mingled with, and followed the specific infectious agents. The latter multiplied intensively for a variable period and disappeared, leaving perhaps, a few stragglers behind. Controversies arose as to the significance of the forms observed, and considerable time elapsed before any general understanding and agreement prevailed. Each of the mucous tracts of the body presented its own peculiar problems because of different relations to the exterior and of different functions. The

controversies over the cholera vibrio were prolonged and acrid. Not only did vibrios appear which could scarcely be distinguished from the cholera vibrio, but several different races of the latter came to light. In a similar way for a time dysentery presented numerous obstacles to a solution of the etiology.

While the lower digestive tract is more or less guarded by the destructive action of the stomach secretions upon incoming bacteria, and the small intestine kept nearly sterile thereby, the respiratory tract is open to all floating matter in the air. The deeper portions are in a way protected from invasion by tonsils and adenoid tissues, by tortuous passages, by the ciliary movements of tracheal and bronchial mucosa, and lastly by an active phagocytic function of the macrophages or dust cells in the ultimate air spaces. Nevertheless, one needs only to examine the lungs and the associated lymph-nodes of air-breathing mammals and man to note the large amount of organic and inorganic dust which has escaped all the protective mechanisms, and which is now permanently lodged in the body tissues. The uncontrolled entry and exit of infectious agents via the aerial route makes the respiratory organs of man and animals especially prone to the acquisition of new adaptable forms of parasitism. They are also the last resort of chronic infectious diseases. This is exemplified in tuberculosis. The pulmonary form is the only one which perpetuates the disease, since escape of bacilli from other tissues to be introduced into other hosts is too rare to permit the extra-pulmonary disease to play any significant part in human life. The same is true of the bovine disease. Here the rather rare establishment of tubercle bacilli in the udder offers an opportunity for an intestinal form in the young which, nevertheless, is relatively infrequent.

It follows that the etiology of respiratory diseases will be complex and that a variety of micro-organisms and parasites may gain lodgment and the opportunity to multiply in the many recesses of the respiratory mucous membrane, and each establish its own type of disease. Furthermore, these invaders might enter coöperatively or follow one another, thus adding to the difficulty of accurately analyzing the relation of microbe to the lesions produced. Again the continuous exposure of the respiratory mucosa to all sorts of noxious agents, to abrupt and wide changes of temperature, might so reduce

resistance as to favor the implantation and multiplication of otherwise indifferent parasites.

Pneumonias may be regarded either as the end-product of a variety of non-microbial predisposing factors which give opportunity for the multiplication of bacteria otherwise incapable of initiating the process, or they may be almost entirely the result of microbial virulence. The former group would in general appear sporadically, the latter in epidemic form. Sporadic pneumonias in man are associated with a variety of infectious agents, chief among which are the pneumococci. Epidemic forms are associated with infectious entities such as influenza. The etiology of epidemic influenza has remained a controversial topic in spite of the many centers of research which have dealt with this disease not only in 1889 but especially during and after the World War when material was more than abundant. No clear-cut results upon which all are agreed have thus far been obtained.

No one seems to have thought of investigating the spontaneous infections of animal life in our environment for more than ultrapractical purposes until Webster and his associates¹ began their work on fowl cholera. All species of domestic animals have their respiratory diseases and it would seem that if this enormous material involving a variety of hosts and a still greater variety of micro-organisms could be brought together by some master mind synthetically inclined, the causes of human respiratory affections would literally drop into our laps. However, there are serious impediments to such a gathering of ripe fruits due to our very scant knowledge of the respiratory diseases of animals. This scarcity of accurate information is in its turn due, first, to the indifference of medical science to this field and the general belief that experiments with human infectious agents on animals will solve all problems; and, second, to the institutions and agencies specially entrusted with the study of animal diseases who usually stop when some practical measure appears which promises help in suppression. As one after another of the animal diseases are being suppressed and eliminated by wholesale slaughter, further research into these unique diseases is paralyzed and even prohibited in some instances. We are in the position of the naturalist who finds rare species becoming still rarer and dying out before the wonderful

histories and mechanisms involved in their evolution have been even superficially investigated.

Before discussing certain general aspects of respiratory diseases of interest both to clinical and preventive medicine, I shall take the liberty of reviewing briefly what has been ascertained in the large field of respiratory disease in animals. Scarcely any species which has come under the herding and domesticating operations of man is free from one or more diseases of the respiratory organs. They usually come to light as forms of pneumonia since this is the fatal stage. Only a few of this large group of diseases have been cleared up etiologically. With all, for a time, certain secondary invaders were given first place in the etiologic scheme. The recent studies on distemper in dogs under the Medical Research Council of England by Dunkin and Laidlaw² are illuminating in several directions. The disease is generally looked upon as a respiratory disease and several earlier American workers who found *Bacillus bronchisepticus* in the respiratory passages claimed this rather ubiquitous organism as the cause. The English observers offered conclusive proof of a non-cultivable filter-passing organism as the cause.

The disease manifests itself as a mucous membrane affection, since the nasal and ophthalmic unicosae react. There may be bronchopneumonia and intestinal inflammation followed in some animals by lesions of the central nervous system. The English observers, by breeding the experimental dogs and maintaining a rigid isolation system, were able to produce the disease without the complications observed in the field. The virus appears early in the blood and causes a febrile reaction which subsides to appear a second time. The fever curve suggests a primary infection followed by a secondary dissemination and excretion via the mucous membranes. The local phenomena are dependent on the multiplication of secondary infectious agents possibly resident in the animal or conveyed with the primary virus. Under conditions in which influenza dogs are exposed to a highly virulent type of *Bacillus bronchisepticus* the disease might indeed present itself as a bronchopneumonia. Under conditions in which certain pathogenic intestinal forms are present the same disease might simulate a typhoid-like or dysenteric disease. It would be of interest to know whether the lesions of the central nervous system in this disease are due to localizations of the primary

filtrable virus or to secondary forms similar to those associated with herpes, and invasive only under certain provocative influences. We may thus postulate some injury to the mucous membranes during the multiplication and discharge of the virus in them which favors secondary, endemic, partly parasitic types of bacteria. The lesions of the nervous system may be looked upon as accidental and not a necessary part of the disease cycle.

Another suggestive investigation was made by Gaffky and Lührs³ into an epizootic pulmonary or bronchopneumonic disease of horses. The seat of the primary lesions appears to be the ultimate bronchioles followed by infiltration of the associated alveoli. In these there appears a glairy, translucent, gelatinizing, yellowish exudate together with marked peribronchial cell infiltration and a cellular invasion of the surrounding parenchyma. The exudate is at first sterile. After four to five days, streptococci appear which had been regarded by earlier students as the primary agents. Filtration experiments were not reported. The early exudate placed in the mouth or nasal passages of horses produces the disease. Intermediate hosts or carriers were excluded. It is probable that the World War interfered with the completion of this research which might have led to important results.

Another type of pneumonia which has aroused the interest of pathologists and bacteriologists the world over is known as bovine contagious pleuropneumonia.⁴ It presents features of interest both in their anatomic and histologic as well as their etiologic aspects. Numerous investigators had described organisms, known later as the bipolar *Bacillus bovisepiticus*, as the cause. This organism can be isolated frequently in animals slaughtered in the acute stage from all parts of the diseased lungs in apparently pure culture. In 1898 Nocard and Roux⁵ succeeded in demonstrating the underlying cause of this disease as a very minute organism which failed to multiply on laboratory media. In 1900 Dujardin-Beaumetz⁶ demonstrated both its cultivability and filter-passing capacity. The pathologic anatomy differs from that of other known pulmonary diseases. It is characterized by an involvement of the connective tissue framework of the lungs and only secondarily of the parenchyma. Sequestra are formed either in form of multiple small territories or even entire lobes. The causal organism stands between the ordinary bacteria

which can be seen and cultivated and the filter-passing forms which are neither visible nor cultivable. Its pathologic effects point rather to the bacteria as its true place than to the genuine filtrable viruses. Its mode of entry and primary locus of attack are not known although evidence points to inhalation and deposit in the ultimate bronchioles. An interesting feature of this type of pneumonia is that it has not been reproduced experimentally, no matter how the virus was introduced. When injected under the skin of bovines it produces progressive edematous swellings which may prove fatal, but the localization in the lungs does not take place. However, it produces unquestionable specific resistance to the pneumonic affection.

Sporadic pneumonia is not uncommon among animal life in our midst probably primarily due to various intrinsic and extrinsic non-microbic causes with the associated micro-organisms as secondary agents and doing the chief damage. Among this group should be mentioned certain forms of bovine pneumonia associated with bacilli to which the generic term of hemorrhagic septicemia was given many years ago. They occur under several serologic types of greatly varying virulence.⁷ The most virulent cause a hemorrhagic septicemia, while the others limit themselves to the lungs with or without appearance in the circulating blood. The pneumonic localization is characterized by hemorrhages, exudation of fibrin on pleura and interlobular septa filling subpleural and interlobular lymph spaces with fibrin thrombi. The next stage is polynuclear cell infiltration and filling of parenchyma and respiratory bronchioles with them. The most virulent types usually produce local epidemics wherever carried by sick or recovering animals. Those of lesser virulence are associated with mild forms of respiratory infection and with other primary agents. This bipolar group is represented by a number of races, among which is the plague bacillus, and it takes the same place among domesticated large and small animals that the pneumococci do in the human race.

The pneumonias of laboratory animals which occur in more or less protracted epidemics have not received the attention they deserve. A study has usually been assigned to novices in the laboratories as if the difficulty and importance of the problem were proportional to the size of the animal. The pneumonia of rabbits⁸ associated with a race of the septicemia hemorrhagica group simulates closely the

fibrinous pneumonia of bovines and in its mild stages that of lobar pneumonia in man. The universal pneumonia of the white rat which enters as an important interfering factor in all long-time experiments of this species in genetics and nutrition, has been studied by F. S. Jones⁹ who isolated a close relative of *Bacillus actinoides* as the presumptive primary agent. The difficulty of obtaining animals free from suspicion of the infection, as well as the partial transmitted immunity of the mother, is the present obstacle to further study. Only by raising the young, separated from the mother at birth, and continuing the new stock through several generations, will this obstacle be overcome.

Many years ago I became interested in a continuing epidemic of pneumonia in a small population of guinea-pigs serving as a breeding stock. The details have been published¹⁰ and I am calling attention to a few features bearing on our present discussion. The disease was due to *Bacillus bronchisepticus* which attaches itself to the cilia of the small bronchi and probably interferes with their function. Resulting pneumonic lesions were limited in extent and occurred only in certain lobes. The exudate was mononuclear. After a number of years, through some additions to the population, a pneumococcus was introduced which grafted itself on the bronchisepticus infection. The exudation became polynuclear, the lesion extended to other lobes, and fibrinous inflammation of pleura and peritoneum appeared. The primary agent became obscured in the cultures and might have been overlooked had not the early experience prevented this. Another observation was made on this material. Reversing the usual order, the endemic disease attacked the older breeding animals. Their young remained normal, even when kept with the parents. On the other hand, other epidemics due to *Bacillus bronchisepticus* have involved especially the young and the lesions have been more extensive. These differences may be attributed to degrees of virulence, to environmental factors, and more particularly to acquired resistance of the group. The group of older animals was obviously under the influence of some nutritional disturbance since very extensive fatty degeneration of the liver was common and, in addition, the alveolar epithelium of the lungs was in an advanced stage of fatty degeneration. The fresh food given was carrots only. These winter epidemics largely disappeared during the warmer periods of the year when

grass was fed them. Other conditions remained the same. I have always regarded this endemic as very suggestive. So far as I know no one has reported a similar study. I am inclined to believe that similar environmental causes are operative in the sporadic winter *pneumonias of man*.

Epidemic plague presents certain interesting aspects not so clearly in view in any other disease. It occurs in two forms, the bubonic and the pneumonic. The former is the one investigated by Koch, the latter, supposed to be identical with the Black Death, has been kept under control and has appeared only in small localized outbreaks. The bubonic is evidently of much lower virulence than the pneumonic. The former is rarely transmitted from man to man and its source is the rat. The pneumonic form may be propagated directly since the virus has a cycle, easily carried through in crowded quarters, which usually maintain other unsanitary conditions favorable to the transfer of aerial infection. The pneumonic type has been referred back to the marmot as definite host. This is not unlikely since the pneumonic localization of the septicemic virus suggests certain differences from the bubonic type best explained as due to animal host differences.

Coming now to the most formidable of respiratory diseases of man—epidemic influenza—we find a confusion of opinion concerning the etiology in spite of the enormous amount of investigation now on record. The first epidemic to appear, in 1889, after the beginning of the bacteriologic era gave us the Pfeiffer bacillus so well known to clinical bacteriologists. During the World War there came a revision of accepted views concerning this bacillus, some authorities changing their position and supporting the theory of some filtrable virus underlying the activities of *Bacillus influenzae*, others becoming even more decided than before in their support of the Pfeiffer bacillus. The work of Cecil and Blake¹¹ reported in 1920 demonstrated clearly the pathogenic capacities of this bacillus after its virulence had been highly augmented by passages through mice and monkeys. About the same time Olitzky and Gates¹² were able to bring to light a minute coccoid bacterium, *Bacterium pneumosintes*, which, present in influenza and absent in controls, produced in rabbits pulmonary lesions which gave it a definite standing as an agent of influenza. Although a filter-passer, this minute organism

was cultivable, and hence, at least for the moment, to be classed as a bacterium rather than as "virus." Superior talents working in different parts of the world have obviously not yet agreed upon the etiologic rôle of any demonstrable microbe. It is not improbable that each has contributed a greater or smaller fraction of the whole truth and that it belongs to the future and perhaps to another pandemic to fit these fragments into their proper place.

A contagious disease of swine, known as swine influenza or "flu" and appearing in mass outbreaks, approximates perhaps as closely as any animal affection the general pattern of human influenza. Thus far researches have not formulated the etiologic basis and comments would be premature.*

On the basis of this hurried review of available information, we may postulate at least two types of pneumonic disease with intermediate types graded one to the other. The first type includes the genuine septicemias in which the pneumonic lesion is simply an attempt of the host at localization. This type is highly fatal. It includes plague pneumonia and rabbit septicemia. The type at the other extreme is one whose micro-organism fails to get a foothold in the vascular system. The process of extension is by contiguity and wholly extravascular. The pneumococci and streptococci probably belong here in the majority of cases. Their intravascular position simply indicates a final breakdown of blood resistance rather than an early stage of distribution and secondary localization.

In an attempt to contribute something to the advancement of the problem of respiratory diseases, I gave considerable time to an epidemic pneumonia of bovines ten years ago¹³ and again in 1929 and 1930. It will be necessary for me to go somewhat into detail concerning the disease to make clear any resemblance it may bear to pneumonic lesions in man and to point out some of the difficulties and uncertainties associated with investigations of this group of diseases. The disease has the usual characters of an epidemic in that

* Since the above was written, Shope (*Science*, vol. 73, p. 214, 1931) has called attention to the probable association of a filter-passing virus with a cultivable bacterium as the cause of swine influenza. The filtrable factor produces only a mild disturbance which becomes akin to the spontaneous disease when the bacterium is associated with the virus. A similar phenomenon has been reported for the common cold by A. R. Dochez and associates (*Proc. Soc. Exp. Biol.*, vol. 28, p. 513, 1931).

cases appeared massed during a given period with a few stragglers closing the outbreak. The beginning and the end of the outbreaks remain unknown. They could only have been determined by the slaughter of many valuable animals. That many may have had a mild attack and recovered cannot be gainsaid since the temperature was not taken regularly. Of the forty odd cases studied recently, one-fourth died and the rest were slaughtered. This afforded an opportunity to see a variety of stages not otherwise accessible, since the spontaneous deaths presented a monotonous uniformity of lesions. The disease in its acute stages is one of the 2nd month of life. One fully developed case was encountered as early as the 19th day. Rarely chronic survivors are detected in the 3rd and later months. Obviously the age cannot tell us what stage the disease is in, since this depends on the time of infection. It happens, however, that calves are exposed early and this leads to a certain uniformity. It is not known that infection of the upper respiratory tract preceded or gave rise to the pulmonary lesions. In a few animals the nasal cavity and sinuses were involved in a catarrhal inflammation.

In most animal pneumonias the smaller lobes, occupying the cephalic half of the lungs are the primary seat of disease. So with this form of pneumonia. These lobes are both the most dependent in the standing position of the animal as well as the less expansible. They thus correspond to the upper lobes in man in one particular and to the lower lobes in another. They also indicate that gravity is a factor in the dissemination of infectious matter. The other half of each lung is made up of the large caudal or diaphragmatic lobe, most expansible and, in the standing position, highest up in the thorax. This lobe becomes involved in the region adjoining the smaller lobes, and the disease tends to creep backward and upward by aspiration of catarrhal products, until fully two-thirds to three-fourths of the bulk of the lungs is no longer functioning. In this stage the animal dies.

Much variation is found in the killed animal in regard to the distribution of the pneumonia. Lesions are limited most frequently to the right cephalic lobe, a territory having an unpaired bronchus, entering the trachea cephalad of the bifurcation. It is thus the first to be reached in any aspiration of infectious matter. The other small lobes may be affected irregularly or symmetrically. In the dead

animal all small and a variable portion of the large caudal lobes are airless. There is no general pleuritis. The lung tissue on section, and viewed from the pleural surface, is mottled with regularly and closely set grey to whitish round areas up to one millimeter in diameter or else uniformly reddish. In nearly every case there were found necroses or abscesses, sometimes only a few, sometimes many involving most of any one lobe or scattered through the entire pneumonic territory. These varied in size from microscopic foci to sequestra several centimeters in diameter. In killed animals the trachea was clean but the air tubes of the affected lobes were covered with a thin, viscid layer of puriform character. In dead animals the entire bronchial tree was deeply congested and covered with a thin layer of pus in which were opaque white flakes.

The histologic picture of this disease is of interest in that it represents a process not thus far clearly seen or described. It has some contacts with the very chronic bovine pleuropneumonia on the one hand, and with the acute pulmonary complications of human influenza on the other. As is common in epidemic manifestations of infectious diseases, the pneumonia under consideration presents various stages due to varying susceptibilities of the animals. There is an acutely fatal, a chronic, probably recovering, and an intermediate type. Each has its own pathologic expression. The focal necroses, nearly always present, indicate a primary dissemination of the infectious agent. The more or less rapid multiplication of the virus in these foci determines the fate of the animal. From these it is disseminated and leads to the second most conspicuous stage of the disease. The congested parenchyma becomes filled with polymorphonuclear cells. These give the lungs a regular mottling of whitish areas about one millimeter in diameter on a reddish ground. This secondary pneumonic infiltration having lobar character may involve three-fourths of the lung tissue at one extreme and only a single lobe at the other. In some instances only necroses becoming encapsuled were present. The general pneumonic infiltration did not follow.

In tracing the etiologic factors cases giving the clearest histologic picture of the disease process are those midway between the acutely fatal and the more chronic cases. In them a peculiar process is evident in air tubes less than 0.1 millimeter in diameter. There is a bulging of the subepithelial tissue into the lumen with loss of covering epithelium of the bulging portion. The intruding mass is made

up of cells with small pycnotic nucleus and abundant cytoplasm. This is densely filled with very minute, rather feebly stained coccoid bodies. The bacteria thus appear in large intracellular masses, ready to be thrown out into the bronchiole and mingle with the polynuclear masses already on hand (Figs. 1 and 2). The stage described soon disappears to give way to an invasion of fibroblasts into the bulging tissue. This becomes organized and covered with epithelium. The lumen of the air tube may remain as a lunar slit or it may be fragmented into three or four small tubes, each lined with columnar epithelium. The peribronchial tissue is broadened by infiltration of monocytes and plasma cells. The large numbers of minute bacteria in this lesion are not the result of postmortem multiplication, but are seen repeatedly in the lungs of animals killed when only unthrifty and slightly dyspneic.

The next group of cases best adapted for a demonstration of the associated bacteria is the group of acutely fatal outcome. Here the process described is universal and involves the alveoli as well as the smallest bronchioles. There is an outpouring of mononuclear elements, probably in part alveolar epithelium embedded in a matrix tinted feebly reddish in which are cloud-like masses of the minute bacteria. This characteristic reddish material is probably a mixture of mucus and necrotic cells. All exudate cells in this early stage have irregular, jagged, pycnotic nuclei or else fail to stain. Polynuclear cells are not yet present in mass. Later cases with less extensive involvement of the lung tissue may appear merely as a lobar pneumonia associated with polynuclear leukocytes. The deformation of the bronchioles then is found only after long searching of sections. Lastly, rare cases exhibit what may be called a hemorrhagic type, in which the necrotic foci are hemorrhagic in character and up to several centimeters in diameter.

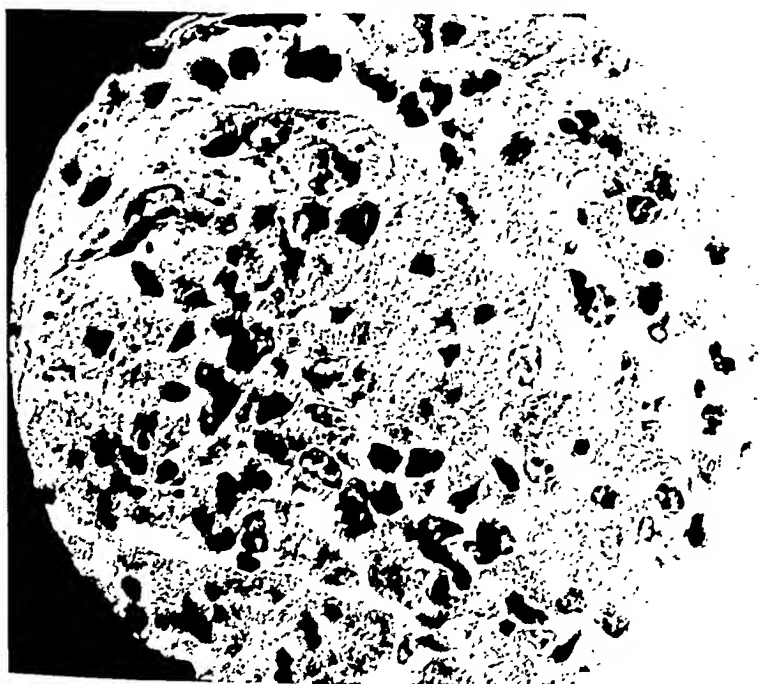
The description of the specific lesions of the bronchioles leaves untouched the original starting point of bacterial multiplication. The histologic details suggest a subepithelial multiplication with secondary destruction of the covering epithelium. This hypothesis involves the question of how they reach this region, whether through destruction of the epithelium from the lumen of the bronchioles, or starting from the alveoli through deposit in the peribronchial lymphatics, or distributed from some primary necrotic focus through the

FIG. 1.



Section of the lung of a calf fifty days old when killed. Autopsy revealed an advanced case of pneumonia with over two-thirds of lung involved. The section passes through a small abscess, about 0.02 millimeters in diameter, in which a large ingrowth occludes the tube. On each side of the intruding mass the alveoli are filled with polymorphonuclear leukocytes. (X 140.)

FIG. 2.



An enlarged photomicrograph of near the center of the ingrowth of Fig. 1. Among the irregular, distorted nuclei of the cells are cloudberry masses of minute coccoid bacteria. These appear to be within the cytoplasmic masses of the cells. Fast and polychrome methylene blue. (X 1000.)

vascular system. Nothing definite on these questions can be stated until more lungs in very early stages have been studied. The genesis of the necrotic foci has not been cleared up, largely because, being the earliest lesions, they are already encapsuled when the secondary pneumonia brings about the symptoms which prompt the slaughter of the animal. Basing ourselves on what goes on in the lesions of the bronchioles, we may postulate a similar intrusion into the vascular areas from the peribronchial tissue. This would most probably lead to thrombosis, associated with a greatly stimulated multiplication of bacteria thereby assisting in the tissue necrosis.

Coming now to a study of the associated microbic flora we find that in cultures from the three different outbreaks studied, three species of bacteria were present, but not in every animal. The combinations varied from case to case. There were present:

1. *Bacillus bovisepcticus*. This species is a widespread inhabitant of the respiratory tract in catarrhal conditions as well as in acute hemorrhagic pneumonia. It has many relatives in mammalian pathology, among them *Bacillus pestis*. It takes the place of the pneumococci in animal pathology.

2. *Bacillus pyogenes*. This species is a minute, Gram-positive, slender rod peculiar to animal life and found in various species in extensive suppurative processes to which it is probably secondary.

3. *Bacillus actinoides*. This form I described in 1920¹³ as a new species and as the probable underlying cause of epidemic calf pneumonia. It is peculiar in that in a special culture medium—coagulated blood-serum to which a small quantity of serum water has been added as condensation water—it appears with huge capsules which simulate the myelin forms found in expectorated alveolar cells of the lungs. Especially characteristic is its growth in serum water. Large flocculi up to one millimeter in diameter develop in it. The fluid itself remains clear. Here the capsules in the form of a radiating mass of terminal clubs are particularly striking. On the surface of this medium, the organism forms minute colonies rarely more than $\frac{1}{2}$ millimeter in diameter. The organism itself is very minute. It fails to multiply on ordinary agar even when bits of lung tissue are present. On agar, plus some whole blood, it may or may not produce a faint film between agar and glass easily overlooked and not transferable except after prolonged cultivation on coagulated blood-serum.

When it multiplies on blood agar capsules are not formed. In the tissues fixed in Zenker's fluid, the organism appears in clouds of minute coccoid bodies staining but feebly in polychrome methylene blue and in Giemsa stain. Rarely, filaments and roundish bodies suggesting capsules are seen.

Since the early published description of this species no other publication concerning this new form has appeared. F. S. Jones⁹ isolated a related species, at least so far as capsule formation is concerned, from the bronchopneumonia of the white rat of the laboratory. It may be readily overlooked unless special culture media are employed and certain early fulminating cases of the disease encountered. In the late stages of repair it may be absent or masked by overgrowth of *Bacillus bovisepiticus* or *Bacillus pyogenes*. That it is the fundamental factor in calf pneumonia is supported by the following facts: 1. Its occurrence in pure cultures from early acute cases when various media are employed to detect other forms. 2. Its dominance in moderately severe cases. 3. The frequent absence of one or the other or both of the secondary types of invaders in cultures. 4. The production of necroses and encapsuled abscesses following intratracheal injection of pure cultures. 5. The frequent presence of the two secondary species in herds in the absence of calf pneumonia.

We are now prepared to ask the question whether this study is of any assistance in the interpretation of data gathered from the human epidemic disease. Directly, I should answer no; indirectly, yes. A few of the suggestive features may be briefly touched upon. Concerning the microbic cause or causes it is obvious that there are rather formidable technical problems to be solved. If we apply the original Koch rules, or at least the substance of these rules, for the demonstration of etiologic relationships to the difficulties, they will stand out quite clearly. These rules were well adapted to the early days of bacteriology when the microbic forms studied were relatively large and their morphology rather stable. This is especially true of the classic disease of the early workers—anthrax. Here the culture and tissue or blood form agreed very closely. Similarly, streptococci and staphylococci could be identified in lesions. When we come to the minute forms, it becomes impossible definitely to affirm that a given form in the diseased tissues is identical with the form in our cultures,

unless some highly specific stain is available. In many infectious diseases, the microbial elements are so scarce that they cannot be demonstrated in certain stages with any degree of assurance. They may be so minute, and absorb dyes so slightly, that tissue granules are easily mistaken for them. Even the microscopic demonstration of undulant fever bacilli in the tissues of diseased guinea-pigs is rarely crowned with success, and when under these circumstances what appear to be bacteria are encountered, the question of artifacts immediately arises. On the other hand, under certain conditions, governed by the length of the disease period, cultures are always positive and pure. Again, the minute bacteria may have several form stages. This seems to be true of *Bacillus actinoides*. In the capsulated form it exists as a slender rod or filament which, in some preparations, is seen segmented into coccoid forms. On culture media, aside from blood serum, when *Bacillus actinoides* can be made to multiply, it does not have the capsule. It then appears as a minute bacillus with coccoid forms coming later, which I interpret as extremely short segments of the filaments as seen on coagulated serum.

The probability that certain bacteria have form cycles has been frequently discussed and a large amount of painstaking observation is now on record. If the minute species appear now as rods or filaments, now as short coccoid bodies, the uncertainty of identifying forms occurring in tissues with those in cultures becomes very great. Certain morphologic stages occurring in tissues may fail to appear in cultures at all, or the reverse may be true—that growth forms, or fructification stages, suppressed in the host tissues, appear in cultures.

The second Koch rule, that organisms found in diseased tissues must be cultured pure, also presents difficulties. The number of minute organisms which can be cultured, but only on special culture media, is not small. They are likely to be encountered at any time. Organisms like *Bacillus actinoides* have little to distinguish them from other minute forms in the microscopic picture. Even in the culture tube minute forms are with difficulty differentiated. When forms can be clearly distinguished by qualitative differences on special culture substrates, such as multiplication on the one hand and failure to grow on the other, or when certain species produce recognizable and peculiar lesions in inoculated animals and may be puri-

fied by animal passages, the difficulty of identification and purity of culture are greatly reduced.

The experimental reproduction of disease with pure cultures demanded by the third rule is likewise fraught with technical difficulties. For human diseases the use of monkeys and the higher apes has reduced some of the obstacles. But the production of the identical disease as found spontaneously remains a pious wish in most cases. Septic diseases lend themselves most readily to reproduction by pure cultures but even here certain factors control the situation. The reproduction of animal diseases would seem to offer greater promise of success, but here also a number of factors must be controlled, and even then the induced disease may be abortive, because rapid attenuation may proceed with cultivation to the necessary stage where the possibility of transferring filtrable agents has been eliminated. In the small number of experimental inoculations of *Bacillus actinoides* into calves, the lesions produced represent the first focal, necrotizing stage only. This failure to produce the lobar disease may be due to attenuation of the culture or to an already high resistance of the animal.

Assuming, then, that we have obtained in pure culture two or more species more or less constantly present in a given epidemic disease, the next step is to find their respective place in the etiologic scheme. If, as occurred in the study of the calf pneumonia, one form, *Bacillus actinoides*, is frequently present in acute cases to the exclusion of one or both of the other two species, the odds are in favor of *Bacillus actinoides* as the primary agent. If it is also known that one other species is a frequent parasite of the respiratory mucous membrane and the other a common pus-producer in other regions of the body, and if *Bacillus actinoides* has not been isolated from normal lung tissue, the evidence that *Bacillus actinoides* is primary is greatly strengthened. There still remains the question whether some non-cultivable, filtrable virus underlies the *Bacillus actinoides* processes. While the evidence against this assumption is strong, it is not conclusive. The following table presents a synopsis of eleven consecutive cases recently studied and the bacteria which appeared in cultures. In only one animal, *Bacillus actinoides* was not recovered. The large necrotic foci favored the multiplication of banal

TABLE I
Eleven Consecutive Cases of Pneumonia

No.	Killed or Died	Age	Extent of Disease	Type of Lesion	Bacteria		
					<i>B. actinoides</i>	<i>B. bovisepiscus</i>	<i>B. pyogenes</i>
1682	Died	56 days	$\frac{3}{4}$ of lung	Smooth consolidation	++	+	-
1684	"	20 "	$\frac{3}{4}$ " "	Two large necrotic foci; smooth consolidation	?	-	++
1687	Killed	5 mos. 9 days	Small areas	Abscesses and collapse	+++	-	+
1688	"	33 days	$\frac{2}{3}$ of lung	Smooth consolidation	+++	-	-
1689	"	45 "	$\frac{2}{3}$ " "	Many necrotic foci	+++	-	+
1690	"	40 "	$\frac{1}{2}$ " "	Smooth consolidation; some small necrotic foci	+++	-	+
1691	"	30 "	$\frac{1}{3}$ " "	Hemorrhagic foci	+++	-	++
1693	"	5 $\frac{1}{2}$ mos.	$\frac{2}{3}$ " "	Necrotic foci	+++	++	++
1699	"	28 days	$\frac{1}{4}$ " "	" "	+++	+	+
1700	"	54 "	$\frac{3}{4}$ " "	A few small necrotic foci	+++	+	-
1703	Died	35 "	$\frac{2}{3}$ " "	Smooth consolidation	+++	(coccus)	+

forms accidentally present and tended to suppress or conceal *Bacillus actinoides*.

In the investigations of epidemic influenza much stress has been placed upon early fulminant fatal cases in evaluating bacteriologic data. This emphasis, it seems to me, is quite valid if the case is uncomplicated. It may also happen that such highly susceptible types at the same time favor other bacteria, and that such cases may fail to bring unequivocal data to the surface. In other words, no one instance can decide so momentous a question, since geographic influences, the stage of the epidemic, whether early or late, must be considered besides individual factors such as the time elapsing since death, associated infections in other organs, and the like.

The brief summary I have presented of the human and animal infectious diseases of the respiratory organs, clearly shows the same tendency to multiple infections throughout, and the resulting confusion which may arise in attempts to assign the proper place to such infections, both in the original incitement to disease, and in the lesions and disturbances which may be ascribed to each. There is a certain significant regularity in the appearance of the same infectious agents in widely separated epidemics needing interpretation, as, for instance, in human influenza and the bovine form I have outlined. It is, furthermore, a significant fact in the history of our developing knowledge of all these diseases that what we now regard as the secondary infectious agents have invariably been proclaimed as the primary and sole agents by early bacteriologists. A point to be borne in mind in evaluating work done on the same disease in different countries is the probability that the same species of micro-organism may appear under slightly different growth forms so that it may be cultivable in one area and not in another and even in the same territory appear under both non-cultivable and barely cultivable races.

We are now facing another revolution in view of the mounting number of diseases associated with and demonstrably due to filtrable organisms. In fact, we are now standing within the threshold of a period similar to that when Koch brought forth his new methods. The confusion and uncertainty concerning etiologic factors were then replaced by satisfying generally accepted explanations of the new discoveries. Similar uncertainty and confusion of today are

being allayed by the results of filtration experiments covering many diseases. In truth, we may be even a little hasty in throwing overboard facts which have had a fairly secure place for nearly half a century. Filtration must, however, be given a thorough trial in all diseases in which visible and cultivable organisms leave doubt either because there are several claiming recognition or because none reproduces the natural disease precisely or because it is not always detected or because the disease varies much in its clinical manifestations.

Studies of disease are oriented in one of two directions, towards treatment and towards prevention. The roads leading to these goals are not identical but they frequently run parallel, merge, and cross one another. The problem of multiple infectious agents so universal in affections of the respiratory tract is a problem of public health as well as practical medicine. For both a thorough acquaintance with all microbic forms associated with respiratory disease is essential. In times of epidemics, the unknown primary incitant may be disseminated with secondary pathogenic forms in the discharges. Or it may meet local endemic infectious agents. In both kinds of secondary agents, virulence may be greatly augmented by frequent passages. In fact, they may in this way become primary during the decline of the epidemic factor. They may, on the other hand, become a force in destroying the momentum of the epidemic factor. It is obvious, therefore, that the solitary quest for the primary inciting agent and more or less neglect of the other agents is not rational. These may play an insignificant part in the beginning and become dangerous elements later on. They may simply represent a disease of a disease, a graft on partly dead tissue, and simply assist the inevitable dissolution, or they may play a preponderating rôle in the evolution of the main injuries. It has been generally assumed that the primary agent injures in some unknown manner the protective tissues and that these injured tissues permit the secondary agents to enter and multiply. This assumption may not include the entire truth and may lead to neglect of dangerous factors. It is highly probable that besides multiplying in exudates and dead tissues, these agents have acquired enough virulence in association with the primary agent to start disease themselves or at any rate to increase greatly the injury produced.

When a pandemic strain meets different local flora the epidemic may assume different expressions clinically and pathologically and the mortality vary accordingly. The wide differences in pathologic and bacteriologic findings reported by observers may perhaps be harmonized if observers develop more detached and less rigid attitudes towards earlier results and inferences and keep in mind the many chances for variation, divergence, and modification of the epidemic and endemic agents. We may, in fact, consider in an epidemic an indefinite number of phyla or lines of succession through which the virus passes, each meeting some slightly different conditions which favor or oppose its increase in virulence. Some are broken off by the isolation of patients. Others continue on their way. Some are lost in meeting resistant individuals. Sooner or later the epidemic declines and is finally extinguished.

The study of the various micro-organisms involved in respiratory diseases creates what may be called clinical etiology to distinguish it from preventive etiology, which is a study of the primary factors tending to disseminate the disease and the suppression of which presumably stops the epidemic. Neither field of work can spare the knowledge gained by the other, but each must specialize to a degree to reach the object aimed at. Preventive medicine is interested not only in the primary agent but also in the secondary forms for reasons already given.

It is obvious, furthermore, that a study of the flora of the normal and the diseased respiratory tract is indicated next to the elucidation of the complete chain of events leading to disease. This chain of events may not be identical the world over in a pandemic. It may be distinctly modified by geographic factors. Though diseases may bear the same terminology in different countries, it does not make them identical. Local factors thrust themselves into the picture which may greatly trouble those who are looking abroad for information about their own problems. It is probably the secondary flora which is responsible for puzzling local phenomena.

The generally accepted admonition to maintain as normal a condition of the system as possible acquires a special meaning in epidemic respiratory diseases. While this admonition has been discounted to meet the current ideas of specific immunity as necessary to ward off such epidemic disease, it remains in force with respect to secondary parasites of the mucous membranes associated with

minor defects. If these are present the primary disease may be more or less re-enforced by an exaggerated multitude of secondary forms already on the spot.

The utilization of data from animal sources may be objected to or discounted by bringing into view the wide differences in the sanitary conditions and environment of herds of animals and human beings. Yet this difference is not so great when we consider respiratory diseases. The herd-like, compressed aggregations of human beings in some of the transportation systems of our large cities cannot be equalled in groups of animals. It is the cities which develop and maintain epidemics and conserve the carriers for future outbreaks.

In conclusion, I would again emphasize the individualization of what we call the same disease in different regions and in different subjects in the same locality. While it is highly important to define certain presumptive causes of disease there is no assurance that when found they may not point to other even more subtle conditions necessary to bring about disease. Pathology needs to be liberalized and relieved from the strain of producing the ultimate culprit in the sequence of events leading to disease. Thus relieved it may be more successful in this very venture than it seems to be at present. We must also accept the statistical rather than the absolute truth. The latter is scarcely attainable as such since its *dissecta membra* are scattered through many individuals and can only be brought together by an act of reason.

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SPONTANEOUS AND INDUCED STREPTOCOCCUS DISEASE IN GUINEA-PIGS: AN EPIDEMIOLOGIC STUDY*

Second Lecture

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STREPTOCOCCUS diseases belong to the group of so-called septic diseases which were the scourge of medical practice before the anti-septic era and which are still active in a subdued, furtive manner, ready to break forth when the routine pressure of aseptic and anti-septic procedures is at all relaxed. Septic diseases usually have a recognizable local start and a septicemic terminus. When the virus remains localized without multiplication in the blood, recovery is usually assured.

The spread of this group of infections is due to some definite, readily traceable act of inoculation, voluntary or involuntary, conscious or otherwise. It differs from such diseases as influenza, for instance, in which the infection is not definitely traceable to any given act or time nor to any precise locality of the body. Epidemics of septic diseases are due usually to some act of man, such as the distribution of streptococcic milk in septic sore-throat outbreaks and scarlet fever, the infection of the puerperal uterus from individual to individual, or the distribution of products from diseased animals, as in anthrax. The fulminant cases occasionally following handling of relatively mild, localized processes have always aroused great interest because of the unexpected virulence encountered.

Septic diseases are well adapted to a study of the relation of local to general processes. They begin locally and gradually or rapidly the resistance of the blood is increased or is overcome and septicemia results. It seems as if the system possessed some naturally present inhibitory substance in the blood which, under the stimulus of the local process itself, may be rapidly replaced and overproduced.

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When the production does not keep pace with the consumption, the host suddenly or gradually fails and the blood becomes more or less flooded with the infectious agent. The restriction of the process in resistant animals to the very places where the immense cellular reaction in the form of abscesses takes place and where we still find the virus when the animal has recovered and after the virus has disappeared from the blood, if it ever had gained a foothold there, indicates that polynuclear concentration does not lead directly to the destruction of bacteria and that its chief effect is to lead the virus outwards by closing in on it and digesting a passage into the open. In the abscesses, the individual bacteria are gradually reduced in number, but this occurs in the culture tube. The conditions prevailing in the abscess do not favor multiplication nor do they point to much more than the gradual dying-out of starved individuals.

To utilize a spontaneous septic disease of animals for what it might reveal seemed promising when such a disease presented itself in the guise of a bubonic affection occurring spontaneously in guinea-pigs under domestication in our laboratories. These animals are naturally exposed to a variety of human infectious agents through contact with attendants and of animal diseases through their food. The material has the advantage in making experiments possible on a species in which the disease occurs spontaneously. This is not the case with human diseases, unless volunteers offer themselves, and as a rule not feasible with a highly and acutely fatal disease. Even in the study of the diseases of animals, the larger the species, the more costly and difficult the undertaking. Another advantage is the important place streptococci occupy in human pathology. Whatever can be learned of any member of this group is, in a sense, a contribution to the entire group.

To give an intelligible account of the experiments carried on with this streptococcus, it will be necessary to present a few facts concerning the spontaneous disease and certain biologic characters of the organism. The disease first appeared in a large population of guinea-pigs in 1907 and was at that time briefly described by Boxmeyer.¹ It spread to other large breeding places at a distance soon after. In Princeton, in 1917, about a dozen diseased guinea-pigs received from another large population were placed in a large box and allowed to breed. The young, when over two months old, were

removed, if not infected, to keep the population down. This small group was maintained until 1926. The disease as it presented itself in the small compound during the nine years was characterized by abscesses which appeared chiefly under the jaw, often in groups of three or more tumors, and reaching a diameter of one to two centimeters before they finally broke and discharged their contents. More rarely the kneefold or popliteal and axillary nodes were involved. Abscesses in the thoracic and the abdominal nodes were occasionally met with. Following discharge, other swellings might appear in the neighborhood or the region return to normal. In all cases the lesions involved lymph-nodes. They consisted in a gathering of polynuclear leukocytes with destruction of the invaded tissues. The resulting pus, like thick flour paste, was finally discharged from a thin-walled capsule. The affected animal was visibly undisturbed in its growth and activities, unless pressure interfered with deglutition, respiration, and reproduction. Large abscesses of the bronchial node nearly filling the thoracic cavity and crowding heart and lungs into a small space were encountered several times. The spontaneous disease is thus a more or less chronic suppurative destruction of lymph-nodes with apparently little disturbance of the general condition. This or a very similar disease of guinea-pigs has been described by a number of observers since Boxmeyers' original paper.² The writers have, in general, limited their investigation to a comparative study of the streptococci encountered. The fact was brought out that at least several distinct varieties of streptococci may produce lymph-node abscesses in guinea-pigs.

In 1926, the immediate stimulus for a study of this affection appeared when the disease seemed to be dying out and when the uncertain method of permitting animals to infect themselves by cohabitation was given up for the artificial method of inoculating pus from animal to animal. It was then observed that in place of producing the bubonic type a rapidly fatal septicemic or pyemic type appeared. No intermediate or less fulminant form was produced. To reduce the fatal issue, pus was gently spread on a shaven area of the abdomen, but this was equally fatal. The animals either died in four to eight days, or nothing happened. When the survivors were again inoculated, they promptly succumbed. Even rubbing it into the unshaven area was fatal in the given period. The same fate

overtaken animals weighing between 300 and 800 grams. Virulence of this strain extended to other laboratory animals. Mice were killed in three days following a subcutaneous injection. Rabbits succumbed to a subcutaneous injection in six days or in less time. The acute fatal disease was characterized by hemorrhagic inflammation and suppuration of the primary, regional lymph-nodes and foci of necrosis and suppuration in the skeletal and heart muscles as well as the diaphragm. These indicated invasion of the blood-stream and perhaps also a virulence sufficient to overcome the resistance of the muscular system usually left intact in septicemias. The streptococci were present in small numbers in spleen and heart's blood in the acute fatal cases, but absent in the bubonic type. Any delay in the acute deaths was usually associated with sterile spleen and blood cultures and beginning localization in the peritoneal cavity. For a time the idea was entertained that some more virulent organism had invaded the small experimental group of guinea-pigs. The reason for surprise at this performance of the streptococcus lay in the usually observed results of the inoculation of cultures of infectious agents which fall far short of the spontaneous activities of the agent. Organisms isolated from cases in which there is widespread involvement of organs and tissues may produce only a local lesion following inoculation.

The micro-organism producing the buboes is a streptococcus. A casual-examination of the pus might lead to the diagnosis of staphylococcus since the organism appears in tetrads, in clumps of ten or more, and in very short chains among the pus-cells (Fig. 1). It is Gram-positive. In agar-slope cultures, the colonies have a peculiar paraffin-like appearance and when well separated tend to flow down the slope in a band as broad as the colony and one to two centimeters long. This flowing is common with bacteria, producing an abundance of capsular substance. Hemolysis is manifested by fresh cultures, but it may disappear irregularly in old laboratory stock. In cultures of different ages, the younger may have lost and the older retained the function. The fluctuating, unstable character of the phenomenon under prolonged artificial cultivation makes this differential reaction somewhat unreliable when old cultures are examined. Dextrose, saccharose and lactose are acted upon with abundance of acid production. Other sugars were not tested. Milk is

coagulated either spontaneously or after heating. No effort was made to find the place of this strain in the culture scheme of streptococci but only those features were kept in view which might have some relation to virulence.

One of the properties of considerable interest is the production of capsules. In the films from abscesses, the halo may or may not be conspicuous but in the abdominal exudate it always is. This exudate is distinguished by a marked ropiness and viscosity and the gross appearance is that of boiled starch. It is always abundant. Abdominal exudates produced by other, non-capsulated strains were liquid, turbid, without any ropiness, and contained curdy flakes and lumps which consisted entirely of leukocytes. The viscosity of the abdominal exudate of this group of organisms may be regarded as evidence of capsule formation. The peculiar gross appearance and viscosity is evidently due to overproduction of capsular substance. The deviation from the chain form, and the clumping in the contents of abscesses and in bouillon may be ascribed to the presence of capsular substance.

To approach the factors involved in the highly virulent inoculation disease, as compared with the chronic, focalized spontaneous affection, the first step to suggest itself was to increase the specific resistance of guinea-pigs by some form of vaccination. To control a highly virulent, fatal disease in a small animal by vaccination is not a promising task. Among the procedures available were (1) heated cultures, (2) attenuated living cultures, and (3) aggressins. Before giving the results obtained by these methods a brief statement concerning the strains themselves is necessary.³

There were on hand three different races of streptococci from guinea-pigs which will be designated A, B, and C. A is the highly virulent strain of our guinea-pigs. During the long period of observation of this organism, various cultures had been isolated at different times. The age of cultivation bears a definite but not absolute inverse relation to the virulence. The strain which has been maintained almost exclusively since 1926 in guinea-pigs by transfer of pus from animal to animal is designated A₃. A₂ was isolated in 1908 from the primary epidemic. A₄ was isolated in 1908 from another large epidemic, probably starting from A₂. A₅ was isolated

from the same population in 1917, and A_7 in 1922. These subcultures were maintained on the ordinary beef infusion-peptone agar.

It is well known that bacteria under prolonged cultivation may become appreciably modified. Among the strains of A such changes have been noted to affect forms of aggregation, hemolysis, capsule formation, and virulence. The substrains A_2 and A_7 had lost hemolytic property. A_3 forms clumps in bouillon while the fluid remains clear. The earlier strains also tended to clump but isolated elements and small clumps kept the fluid partly clouded. The capacity to form capsules was most pronounced in A_8 and diminished in the earlier substrains in order of length of cultivation. The paraffin-like appearance of colonies was still pronounced in A_7 but no longer in A_6 and older strains. Nevertheless, capacity to form capsular substance had not been lost entirely.

The virulence of the older substrains of A was distinctly reduced. That of A_8 has been described. A_7 , cultured since 1922, possesses characters indicating its identity with A_8 . The first subcutaneous inoculations (in 1929) produced local abscesses and suppuration of the first regional lymph-nodes. After some twelve passages through guinea-pigs, pus placed on a shaven area caused abscesses in the nearest lymph-nodes, more rarely in secondary nodes. Death followed regularly the injection of a fairly large dose of culture or pus into the peritoneal cavity. In several animals muscular and cardiac abscesses were found. A_6 cultured since 1917 was more attenuated. Small doses injected into the peritoneal cavity failed to kill. Subcutaneous doses produced a local abscess and suppuration of the nearest lymph-nodes. A_2 and A_4 were somewhat less virulent than A_6 . Large doses into the peritoneal cavity were fatal, however. Serial inoculations into guinea-pigs of A_6 and A_7 failed to bring virulence to the level of the passage strain A_8 .

To sum up the results of artificial culture, we find hemolysis greatly impaired, capsule production much reduced quantitatively, and virulence modified in that the septicemic type following contact with a shaven surface was lost in all substrains. Such contact still caused suppuration in the regional lymph-nodes but this also disappeared. Introducing the virus into the subcutis still affected the regional lymph-nodes. The intraperitoneal injection—the severest test next to intravenous injection—still caused death when the dose

was large. Repeated passages failed to bring even the most recent substrain to the passage level of virulence.

Strain B was obtained in 1927 from Dr. J. G. Hardenbergh⁴ who had isolated it from an epidemic among guinea-pigs in Rochester, Minnesota. The strain had been under cultivation for perhaps a year. B was inoculated into a number of guinea-pigs to determine its relationship to A, because it was at first supposed that the lymphadenitis was due to only one species of streptococci. Strain B when introduced into the peritoneal cavity in fairly large doses was fatal in three to five days. Small doses were borne successfully and used as vaccines later. Subcutaneous injection produced necrosis and suppuration locally and abscesses in nearest lymph-nodes, more rarely in other nodes also. The essential difference between it and A was the apparent absence of capsular substance. This difference manifested itself in the peritoneal exudate following direct injection into that cavity. All the substrains of A when causing death give rise to an abundant exudate resembling boiled starch and are highly viscid in consistency. The exudate produced by B was non-viscid, flaky or curdy. On the other hand, B produced the same type of hemolysis as A.

C was isolated by the writer from a large suppurating lymph-node in the submental area of a guinea-pig. This strain was non-hemolytic. It was fatal when injected into the peritoneal cavity in fairly large doses. The exudate was non-viscid and flaky with a tendency towards hemorrhage. Rubbing on a shaven area failed to produce lesions locally or in the nearest lymph-nodes.

To reproduce the bubonic type, it was regarded necessary to develop a group of specifically resistant guinea-pigs. It is unnecessary to go into much detail concerning the various efforts made to bring together such a group. The first experiment was made with heated cultures of Strains A₈ and B. The surface growth of agar cultures in Blake bottles after two to three days' incubation was washed off with bouillon and the suspension heated at 62°C. for thirty minutes. The turbidity was adjusted to 1.5 of the Gates scale and about two cubic centimeters injected into the peritoneal cavity at intervals of seven to nine days. The number of injections varied from two to four. The final test was made by gently spreading pus from an abscess of an acute fatal case over a shaven area, about one centimeter square

on the abdomen. No resistance was produced in any of the animals. The next step was to use living attenuated cultures. To avoid if possible any local immunization, the injections were made into the peritoneal cavity. A slight discharge of infecting material into the wound produced by the needle could not be avoided, and as a rule slight swelling of the regional subcutaneous lymph-nodes resulted. The cultures used were Δ_2 , Δ_4 and Δ_6 , and Strains B and C. It would be going too far to enter into the interesting history of these animals. Only a few essential points can be brought out. The dose of culture material used was varied in accordance with information gained in earlier injections. The full-grown agar growth was washed down into the condensation water (about one-third to one-half cubic centimeter) and of the resulting turbid suspension from one-tenth to one loop was suspended in one cubic centimeter salt solution or bouillon before injection. The loop carried about $1/250$ cubic centimeter. A second injection followed with a dose three to five times as large as the first. The period elapsing between the two doses was determined by the condition of the animal, and this in turn was judged chiefly from the weight. Some of the animals died as a result of the vaccination. A number, however, weathered the vaccination successfully and had gained up to 300 gms. in weight when the test inoculation with Δ_8 was made. This was not made on all guinea-pigs at the same time owing to the different rates of recovery from the vaccination. However, with each inoculation a control was included which in all cases succumbed within three to eight days. By this method there had been produced several cases of the bubonic type by raising the specific resistance. This outcome may be contrasted with the results of serial cutaneous inoculation of pus extending over a period of four years. During all this time not a single case was produced. All inoculated animals died of the acute septicemic form.

The surviving guinea-pigs presented a variety of pathologic conditions, except the one treated with Strain B which developed no lesions. The animal treated with Strain C, a strain differing materially from A and B, was slightly protected as indicated by a somewhat prolonged life and only local lesions at the autopsy. Some localization in the central nervous system may have caused death. One animal approached most nearly the early spontaneous type of lymphadenitis. It was not examined soon after the final test inocu-

lation to note any regional lymph-node involvement, owing to the writer's absence. Sixty-five days after inoculation an abscess had developed under the right lower jaw bone. Twenty-seven days later, there had developed three abscesses under the lower jaw, one in the right axilla and one in the right groin. The weight at this time was 735 gms. It was chloroformed three months and three days after inoculation. The autopsy showed three abscesses in cervical region, each about one centimeter in diameter, besides three to four slightly swollen lymph-nodes. The contents of the abscesses was a soft, consistent mass coming out tape-like when the abscess was compressed. The axillary abscess had discharged and collapsed, leaving a small scabbed-over area. The viscera were normal. Films of pus contained one or two small groups of minute cocci of variable size in a microscopic field with a rather variably intense stain. Cultures of bits of spleen and liver and of drops of blood remained sterile. Cultures of pus from the abscessed lymph-nodes developed into continuous films of colonies.

To increase the number of resistant guinea-pigs, a third experiment was carried out with living cultures as vaccines. The same strains were used, namely, A₂, A₄, A₆, and B and C. The methods described in the preceding experiment were used with slight variations in dosage. Two guinea-pigs were treated with each vaccine. Following the second vaccinal intraperitoneal injection, all animals were subjected to a cutaneous inoculation with pus from an abscess of an acute fatal case in the inoculation series of A₈. Both animals treated with A₆ and those treated with C succumbed to the acute type. No appreciable resistance had been produced. One of the pair treated with A₄ died, the other and both animals of the A₂ and the B pair survived. Owing to a local abscess and suppuration of the nearest lymph-node as a result of the first vaccination, one animal was not treated a second time. It survived the final test with swelling and abscess formation in both popliteal chains of nodes. Of the five survivors, four developed swellings and in part, suppuration of the nearest popliteal lymph-nodes. The fifth (No. 22) developed a number of abscesses and finally succumbed.

No. 22. Nov. 4, 1929. Weight 325 gms. Receives into peritoneal cavity 1/10 loop (1/2500 cubic centimeter) culture of A₂.

Nov. 18. Weight 400 gms. No local swelling. Receives one loop culture as before.

Dec. 7. Weight 515 gms. Gently spread on shaven area of abdomen one loop of pus, diluted in bouillon, from an acute fatal case.

Dec. 24. Weight 565 gms. Scab on side of inoculation. Right popliteal node one centimeter in diameter.

Jan. 9, 1930. Two nodes in right popliteal region swollen. One discharging pus. Fairly numerous clumps of cocci in this pus.

Feb. 7. Weight 670 gms. Slight induration in popliteal regions.

March 3. Abscess in lymph-node on right side of neck two centimeters in diameter. Another over lower ribs, a third over dorsal spine, evidently in muscular tissue. Animal active.

March 13. Guinea-pig aborted; is sick.

March 14. Lying on side, very quiet. Chloroformed. The following lesions were found:

Abscess in lymph-node of cervical region two centimeters in diameter, two others bean size. Contents purulent, can be squeezed out, tape-like. One abscess in muscular tissue over lower ribs. Deep inguinal node, two to three centimeters in diameter. Contents puriform. Abscess in fat deposit over upper dorsal vertebrae, one centimeter in diameter. Viscera normal, except uterus, which is deeply congested.

Attention is called to the fact that the crop of abscesses appeared nearly three months after the inoculation with virulent pus. Cultures of blood and a bit of spleen each developed a single colony of the streptococcus. Cultures of pus from abscesses contained many colonies.

Guinea-pig No. 17 gave birth to three guinea-pigs, two of which were subsequently tested for a passively transmitted resistance.

Nov. 4, 1929. Weight 320 gms. One-tenth loop of Strain B injected into peritoneal cavity.

Nov. 18. Over point where needle pierced abdominal wall, a firm subcutaneous swelling with base one centimeter in diameter. Right popliteal node three-fourths centimeter in diameter.

Dec. 3. Weight 450 gms. Minute ulcer tips abdominal swelling.

Dec. 13. Weight 505 gms. Right popliteal node about one centimeter in diameter. Local lesion has a small scab over it.

Jan. 16, 1930. Weight 725 gms. Popliteal nodes just palpable. No other lesions. Spread on shaven area of abdomen pus from thymus abscess of an acute case.

Feb. 7. Weight 750 gms. Both popliteal nodes about one centimeter in diameter.

March 2. Right popliteal node still one centimeter in diameter. Left has discharged and is much shrunken.

April 17. No palpable lesion.

April 18. Three young born.

A fourth experiment was carried out to test again the effectiveness of heated cultures. The first test having proved negative, it seemed desirable to try once more. The experiment was modified to the extent of introducing aggressins, or the heated peritoneal exudate of guinea-pigs which had succumbed to intraperitoneal injections. For this purpose the passage culture *A*_s was used. The injection of minute doses of pus from acute cases produced an abundant highly viscid exudate and death in two to three days. The exudate was thinned by introducing normal saline into the peritoneal cavity and pipetting the mixture out. This rather thick, opaque, viscid suspension was heated in submerged tubes at 62°C. for thirty minutes, tested for sterility, and stored in the refrigerator.

Six guinea-pigs were treated with heated suspensions of agar cultures of *A*_s as in the first experiment, and three with aggressin. At the same time, three controls were caged so as to match the ages of the treated guinea-pigs in the final tests. All five immunizing doses, from 1.2 to two cubic centimeters each, were injected into the peritoneal cavity at intervals of nine, eleven, fifteen, and nine days respectively. For the final test the guinea-pigs were divided into three groups and each group inoculated with one control fifteen, nineteen, and twenty-two days after the fifth vaccination. The final test inoculation was done by gently spreading some diluted pus from acute, fatal cases of serially inoculated guinea-pigs on a shaven area of the abdomen.

The weights of the guinea-pigs at the beginning of the vaccination period varied from 230 to 290 gms. The weights at the final test inoculation differed materially. The controls had gained most. With one exception the animals receiving the heated cultures were almost as heavy as the controls. The aggressin group suffered most

from the treatment. Whereas the controls and the culture group gained from 300 to 400 gms., the aggressin group gained about 200 gms.

Looking at the results we note first a difference among the three groups, indicating variation in the test doses applied to the skin. This was to be expected from the use of pus in which bacteria appear in clumps of various sizes. The results, however, are not ambiguous. In the three groups the aggressin-treated guinea-pigs, in spite of low weight, are highly protected. The culture pigs much less so, but still well above the controls in resistance.

Three guinea-pigs which showed no lesions after the first test inoculation were tested a second time.

No. 194, aggressin-vaccinated, was reinoculated after twenty-one days. The right popliteal lymph-node (nearest the shaven area) became swollen and abscessed. No other lesion had appeared two months later.

No. 202, aggressin-vaccinated, was reinoculated twelve days after the first test. In both axillary and the right popliteal node abscesses developed. Two months after inoculation these had disappeared.

No. 200, treated with heated cultures, was reinoculated twelve days after the first test. Both popliteal and both axillary nodes became abscessed. The guinea-pig died nearly two months after the test.

Most of the animals of this group died between three and four months after the test inoculation. This was probably due to the too early test and reinoculation and a too early pregnancy. The inoculation led first to infection of the regional (popliteal) lymph-node and then to the associated retroperitoneal or pelvic node. The pregnancy causing pressure upon this node through enlargement of the uterus most likely led to the dissemination of the streptococcus.

The outcome of the attempts at producing specific resistance was successful in demonstrating that the resistance observed in the spontaneous disease was, at least in part, due to specific immunity. This inference might have been made at the start but it had no experimental basis and there was still to be accounted for the source of the immunity among the guinea-pigs breeding and inoculating one another in the enclosed area. Of the procedures used to produce resistance, the injection of minute doses of living attenuated strains

seven and one-half days. Two out of three vaccinated guinea-pigs died.

A second group of five animals representing two litters born of vaccinated parents was available more recently. Two in one litter were eighty-six days old and therefore considerably beyond the passively immune period assumed to have disappeared at the age of two months. Three from another litter had almost reached the age when transmitted antibodies may be regarded as dissipated. Table I gives the essential data. All young succumbed to the surface inoculation and any immunity would appear lacking. But an analysis of the data brings out certain extenuating conditions. The first litter is considered too old. The second, on the borderline, shows a slight resistance over the first litter and a definite increase over the controls. Moreover, in the second litter the two females were already in the early stages of pregnancy. The male was clearly more resistant than they. The passage virus had obviously become more virulent, as witnessed by the depression of the life period of the controls to three and one-half days, the lowest of the entire four-year period. Finally the adults (parents) had probably lost some immunity since there had been no evidence of buboes among them for some time.

TABLE I

No.	Weight	Age	Result of Test Inoculation	Average for Each Group
323	<i>gms.</i> 515	86 days	Dead in 6 days	4 days, 21 hours
324	555	86 "	" " 3 " , 18 hours	
353	500	48 " (male)	" " 7 " , 9 "	5 " , 21 "
354	455	48 " (pregnant)	" " 4 " , 22 "	
355	480	48 " (pregnant)	" " 5 " , 9 "	
382	420	Control	" " 3 " , 18 "	3 " , 12½ "
395		"	" " 3 " , 7 "	

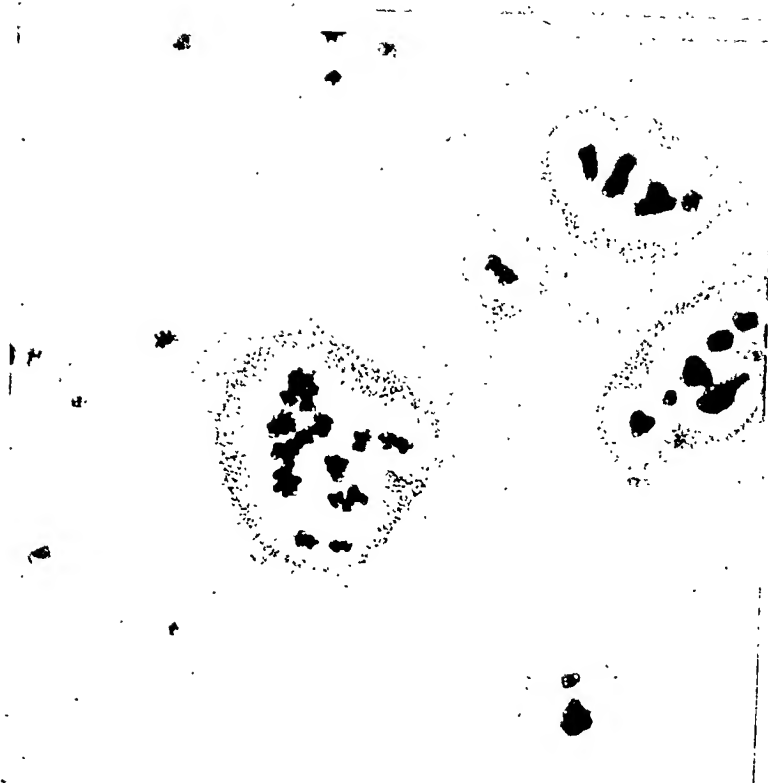
Although the data bearing on this phase of the subject are few and need repetition, the experiments are clear-cut in view of the fact

FIG. 1.



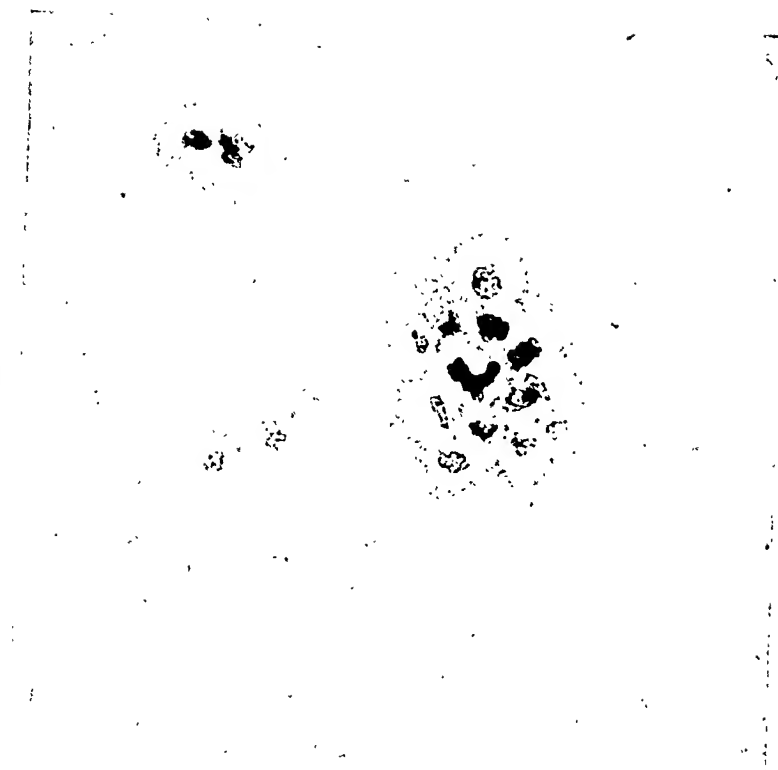
Film of pus from an abscess in muscular tissue (acute fatal type), stained in alkaline methylene blue. The streptococci appear as clumps, surrounded by a halo and bordering this a feebly stained zone or ring. (x 940.)

FIG. 2



Film from a twenty-four-hour agar culture of peritoneal exudate, stained in alkaline methylene blue and photographed mounted in water. (x 940.)

FIG. 3.



Film of the same exudate, stained in the same way, dried and mounted in balsam. (x 940.)

that in the long series of inoculations from guinea-pig to guinea-pig from an unexposed population to maintain the virus, no resistance was noted in any animal. Earlier experiments with the young of an unexposed population had shown no resistance. Attempts to develop a partly resistant population of breeding adults are being continued with the hope of bringing out the factor of transmitted passive immunity in the young more clearly.

The Relation Between Capsules, Phagocytosis and Virulence.—Some relation exists between these factors which, however, it has been impossible to formulate satisfactorily. Many films of the contents of abscesses and exudates have been examined in the course of this study. It has already been stated that the cocci occur in clumps and that these are surrounded by halos of various widths. The cocci themselves tend to vary. In pus they are usually smaller than in peritoneal exudate. It is probable that the capsular substance may be digested by polynuclear leukocytes as fast as it is formed. In the peritoneal cavity the stimulus to form capsular substance may continue while this substance may not be subject to rapid disintegration or digestion. This tendency of capsule formation or accumulation as indicated by a highly viscid exudate may be especially strong in the guinea-pig. Pneumococci of guinea-pig origin develop very large capsules in the peritoneal cavity. Wherry and Lamb mention the viscosity of the peritoneal exudates in experimental animals inoculated with *B. tularensis*. The variable condition of the capsule may explain the difference in size of the stained cocci frequently observed. One other condition is seen in the cultures from guinea-pig tissues. In any clump some stained cocci may be twice the diameter of the rest. This increase in size if referred to a capsule would mean a different one from the unstained halos in exudates. The possibility of two capsular substances of different make-up, one more easily lost in cultures, may account for the conditions observed. When stained films are examined in water the outlines of the individual cocci are fairly well preserved. After the film has been dried and mounted in balsam the cocci appear as if melted together (Figs. 2 and 3).

Phagocytosis has not been observed in exudates due to passage strain A₃. It has, however, been frequently noticed in the culture substrains of A. Frequently there are signs of actual multiplication

or minute colony formation within leukocytes which indicates a certain vitality of the intracellular forms. Phagocytosis is present when exudates are due to Strains B and C. Neither of these produces a viscid, boiled-starch-like peritoneal exudate. The capsular substance may thus be a factor in the establishment and maintenance of a high degree of virulence. Virulence of a lower degree exists without evident capsules, as shown by Strains B and C.

The aggressin immunity established in the fourth experiment confirms a number of earlier workers under whom aggressin vaccination of a number of animal diseases has been put into practice. In the present experiment, the superiority of the aggressin may be ascribed to the very great increase in capsular substance in the peritoneal cavity, as compared with the culture tube.

A Comparison of Bubonic and Septicemic Pus.—The streptococci in the acute fatal disease are not restricted to the lymph-nodes as is true for the bubonic type, but abscesses containing cocci in large numbers appear in the skeletal muscles, and in the heart, diaphragm, and thymus. The only nodes visibly abscessed in the short period between inoculation and death are the nearest popliteal nodes. The cocci in the abscesses of the bubonic disease are relatively few in number when compared with the pus from any focal lesion of the acute disease. Streptococci circulate in small numbers in the blood of the acute, but not in that of the chronic type. The cocci in the bubonic disease remain and multiply in a system which is not only fairly resistant at the start but which increases its resistance as the disease progresses. One might postulate some difference between acute and chronic pus besides what is implied in the difference in mere numbers. The cocci meet an increasing resistance and may undergo certain changes whereby they are protected while ceasing to multiply. The condition may cause a delay in multiplication when the cocci are placed in a new medium. This may be described best as a lag in the multiplication of the bubonic strain. The septicemic cocci are in an active state of multiplication which goes on when pus is transferred to a fresh subject. The lag may be due to a certain condition of the cocci imposed on them by the host reaction. It may be a physical condition involving the function of the capsule or it may be due to associated antibodies carried in the pus. It has already been stated that the primary cultures of bubonic pus

are as virulent as those from acute cases. During multiplication in the primary culture the cocci may have thrown off whatever causes the lag, and they now go on as in the acute type. The theory of lag is supported by the following experiment:

Pus from an acute fatal case was ground up with bouillon and dilutions of this mixture prepared equivalent to one-tenth, one-hundredth, and one-thousandth. In grinding pus, the clumps of cocci are in part disintegrated and the number of colonies obtained by culturing such dilutions may be as large as, or even larger than the parent dilution. Cultures of the one-thousandth dilution contained more colonies than those of the one-hundredth dilution. Guinea-pigs were inoculated with a loopful of each suspension gently spread on a shaven area. At the same time two guinea-pigs were inoculated as described with the one-hundredth and one-thousandth dilution, and in addition the coated surface of the skin was pricked twice with a hypodermic needle without adding any infectious matter. The pricks were intradermal and about two millimeters in length. Table II gives the results. The intradermal pricks deposited a certain minimum amount of the surface dose in the cutis where it could not be rubbed off or otherwise removed from entry into the tissues. Here any delay in multiplication or absorption could not eliminate the virus. Accepting this interpretation we can under-

TABLE II
Surface and Intracutaneous Inoculation

Guinea-pig No.	Mode of Inoculation	Dose	Result
196	Surface	1/10 dilution	Dead in 9 days
289*	"	1/100 "	No effect
290*	"	1/1000 "	" "
288	Surface + needle pricks	1/100 "	Dead in 5½ days
291	" " " "	1/1000 "	" " 6½ "

* A second inoculation with undiluted pus fifteen days later caused death in four and one-half and five and one-half days respectively.

stand why the pus of chronic buboes does not take readily when spread on a shaven surface. There is a certain lag in the activities of the cocci which favors their removal by friction of the body surface or imprisonment in a local scab. To this may be added a cer-

tain slowness of host reaction to the bubonic condition of the cocci themselves. Whatever difference between acute and chronic pus may exist is temporary and due to environment. The fundamental virulence is evidently unchanged.

The two experiments, one producing the bubonic type in vaccinated guinea-pigs, the other demonstrating a similar but slight resistance in the young of immunized females, taken together, provide an explanation why, in a restricted multiplying population of guinea-pigs receiving none from the outside, lymphadenitis due to a highly virulent *streptococcus* should be of the chronic lymph-node type, whereas in guinea-pigs from non-exposed groups the inoculation disease should be septicemic with abscesses forming in heart and muscular tissue.

Applications to perhaps a wider range of phenomena in infectious diseases may be made of the facts presented. These may be of clinic or epidemiologic import. Clinically, the high degree of virulence manifested at times by streptococci may be masked ordinarily by the acquired immunity of those carrying the virus in local lesions. It may also be due to the stage of growth activity of the streptococci, as in terminal infections by this species leading to dangerous postmortem surface wounds from organisms multiplying without lag.

The reciprocal action of streptococci in producing resistance towards races not identical was shown by experiments with Strains A, B, and C. The experiments might well have been profitably extended to other races since the effects are quite clear-cut when produced by a race (A_s) that is acutely fatal to control animals. Such reciprocally immunizing effects should not be lost sight of in the attempts to wipe out so-called local infections. All such infections have a vaccinating action except in those individuals whose power to produce protective antibodies is below par or fails to keep up and get ahead of the local infectious process. Such individuals are, however, always in danger whether carrying local infections or free from them.

In aggregations of wounded individuals there is always danger that streptococci and perhaps other rapidly multiplying organisms may be in the active stage, without lag. In the preantiseptic period these must have been responsible for the epidemics in lying-in hos-

pitals where the hands of man and fomites completed the cycle of these infectious agents, in their most proliferative stage, from individual to individual. The same may be said of other wounded tissues encountered in war hospitals. If left to themselves, the finally discharging fluid would in all probability be less active.

An important question to ask at this point is why septic agents have not been eliminated under the treatment accorded them for many years by antiseptic methods. Is it that agents of low virulence in local lesions may rapidly acquire septicemic power in one or more passages, or is it that agents of high virulence are being imported from regions where antiseptic methods are as yet not widely diffused and where, as a result, the population has acquired a high degree of resistance, or is it due to the rapid changes in populations in the large centers?

The facts presented offer several suggestions in the field of epidemiology. We have noted that the same micro-organism may produce two quite distinct types of disease—a chronic, focal, and an acute, septicemic or pyemic type. In the first, the virus is allowed to ripen, as it were, and become ready for spontaneous discharge. The individual is but little affected. In the second, the virus shut in by death is removed by the hands of the experimenter and artificially planted on a slightly denuded surface. This act causes death promptly. Two different cycles of the virus are thus in operation. The two varieties of virus act differently upon susceptible and specifically resistant animals, producing in the former either death or failure to take, in the second a focal, more or less progressive disease of the lymph-nodes. In a fresh, susceptible population the action of such a virus may produce one or a few sporadic deaths and no more because the virus is still locked up in the fatal cases. A new importation of virus may have the same result. In a small community, therefore, even though susceptible, the imported disease may fail to take root. In a large population, however, after sporadic deaths, the virus will find some resistant individuals which may survive the normal discharge of the virus. The presence of a certain concentration of individuals, presenting a certain relative resistance may be necessary to give the epidemic its continuous existence over a period during which susceptibles are being weeded out and the rest recover.

The second factor in our problem—that of passively acquired re-

sistance in fetal life, or through lactation in its influence on individual and mass disease—has not been given the place that belongs to it in the mapping out of the course of epidemic and endemic diseases. If adults have passed through such a disease as tuberculosis, or if the female is passing through it during gestation, what effect will be exerted on the offspring in the presence of the infection? May not such offspring do better than those which have not had this preliminary intrauterine or lactation treatment when promptly removed from mass infection? Has this factor been sufficiently taken into account in estimating the effect of the Calmette-Guerin vaccination against tuberculosis? These queries are presented here for due consideration in all mass vaccinations undertaken in the earliest months of life.

It has been customary to regard chronic carriers, or those affected with local processes, as equal in capacity to transmit disease to those who are in the active stage of a given infectious disease. That the two conditions are not identical must be granted. Yet it would be going too far to apply our findings strictly to any other disease. The inference to be drawn, however, is that the condition merits special study. Are the typhoid bacilli discharged by a chronic carrier the same, functionally, as those passing out in the active intestinal disease? Unable to answer the question, Public Health must assume that they are until the contrary is proven. Yet research cannot rest content with the assumption of complete identity. The difficulty lies in the absence of methods of sufficient delicacy to be applied to the problem.

CONCLUSIONS

1. A virulent disease of guinea-pigs due to a capsulated streptococcus tended to die out when confined to a restricted breeding group.

2. The spontaneous disease occurred in the form of suppurating lymph-nodes. The mortality was low.

3. When the pus from the chronic, bubonic type was inoculated into guinea-pigs from another, unexposed group, it produced a pyemic or septicemic, acutely fatal disease.

4. There are indications that the offspring of female guinea-pigs which have passed through the bubonic disease possess enough passive resistance to resist early infections to the bubonic type.

5. The intraperitoneal injection of pus or cultures therefrom produced a viscid exudate readily distinguished from that due to non-capsulated races. This heated exudate or aggressin was superior to killed cultures as a vaccine.

6. Pus from abscesses of the chronic or bubonic type contain cocci which are probably in a resting or lag state. Pus from acute fatal cases shows no lag.

7. A gradual reduction in virulence occurs in cultures. The disease produced is restricted to suppuration of the regional lymph-nodes.

8. There is a certain relationship manifested by immunization among streptococci of different types.

9. Stained films of peritoneal exudate, bubonic pus, and primary cultures of these suggest two capsules or a capsular substance in two different states—one closely applied to the cocci and absorbing stain, the other appearing as an outer unstained halo.

REFERENCES

¹ BOXMEYER, C. H.: *J. Infect. Dis.*, vol. 4, p. 657, 1907.

² For a review of the literature up to 1929 see MEGRAIL, E., and HOTT, R. N.: *J. Infect. Dis.*, vol. 44, p. 243, 1929.

³ It should be stated that the guinea-pigs used in this study were from a single population actively interbreeding, into which outsiders had not been introduced for a number of years, and which had not been in contact with this streptococcus disease for at least ten years. The material was therefore as uniform as any closed isolated population.

⁴ HARDENBERGH, J. G.: *J. Lab. and Clin. Med.*, vol. 12, p. 119, 1926.

THE MALARIAL THERAPY OF PARESIS*

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FOREWORD

SOME time previous to December, 1922, my attention had been attracted to the work of Professor von Jauregg, of Vienna, in the treatment of paresis particularly with malaria, and also during that time my friend Doctor Jelliffe, who was traveling in Europe, had written me about visiting the von Jauregg Clinic and seeing this work in progress. During the winter of 1922 my friend Professor Weygandt, of Hamburg, was scheduled to speak on this subject before the New York Psychiatric Society. I went to New York to hear him. I was very greatly impressed with his presentation and subsequently had considerable conversation with him regarding the whole subject. I returned to Washington, having decided to undertake the treatment at Saint Elizabeths Hospital.

The plan which I formulated at that time and which has been carried out since then needs to be commented on only in two particulars. First, I created what was known as a Paretic Board,† consisting of four men who I hoped would combine the elements of therapeutic optimism, pessimism and an intermediate position, whose function would be to examine all patients previous to treatment and from time to time thereafter, keeping a record of these examinations at the three levels, laboratory, neurological and psychological. Secondly, I decided from the first to use only Wassermann-free malaria infected blood donors, as I was not only

* The social problems growing out of the cured paretics to their old environment, and the technic and details of the treatment, will follow by the same writer in the December, 1931, INTERNATIONAL CLINICS.—EDITOR.

† This Board consisted of Drs. S. A. Silk, J. E. Lind, W. W. Eldridge and Philip J. Trentzsch. Doctor Trentzsch shortly afterward resigned and the work continued under the direction of the remaining three members of the Board.

convinced of the possibilities of errors in diagnosis but of the impossibility of explaining away an alleged inoculation of syphilis even though it might not occur. While I am convinced that the danger of transmitting syphilis by inoculating blood for the purpose of transmitting malaria is negligible if not nil, for purposes of expediency I still maintain the practice.

INTRODUCTION*

THE treatment of general paresis has naturally paralled the concept of its etiology. It may therefore be divided into three stages.

I. The Stage of Various Therapy.

(Venesection, blistering, hydroelectrotherapy, tonics, digitalis, quinine and bromides. Alcoholism was considered *sine qua non* at this stage.)

II. The Stage of Syphilitic Therapy.

(Mercury, arsphenamin—by various methods—latest tryparsamide.)

The status of the treatment of paresis in 1917 was that in spite of its known connection with syphilis no remedy had been found which reached the disease in situ and had any favorable effect upon it.

The hopeless picture the disease presented before the advent of malarial therapy is well known to every psychiatrist. It is graphically pictured in Graph 1 (p. 300) which considers the fate of 214 successive admissions to St. Elizabeths Hospital. One hundred and thirty-seven were dead before one year after admission. At the end of three years twenty-six patients were alive and at the end of five years after hospitalization only five patients were still living.

III. The Modern Malarial Stage.

Professor Wagner von Jauregg must be given all the credit for the discovery of this treatment but even he was on its trail for thirty long years before he finally established its therapeutic reality. His first observation was made in 1887. He later experimented with

* Summarized by Dr. S. A. Silk from material prepared by Dr. J. E. Lind.

tuberculin, mercury, and typhus vaccine, finally hitting upon the benign tertian form of malaria as being easiest regulated.

In 1917 he inoculated nine paretics with marked improvement. This method was soon taken up by other European psychiatrists and in December, 1922, it was decided to try out the method at St. Elizabeths Hospital.

GRAPH 1.

214 Consecutive admissions treated without malaria but with arsphenamine

267 died within one year after hospital admission

5 alive five years after hospital admission

0 discharged from hospital as Social Recovery or Improved

192 non-splenic cases treated with malaria

18 died within one year after inoculation with malaria

194 alive 5 years after inoculation

40 discharged from the hospital as Social Recoveries or Improved

A comparison of 192 Inoculated Cases with a Group of 214 Consecutive Admissions who were treated with Arsphenamine but without malaria.

On December 10, 1922, the first patient was inoculated with malaria and incidentally he was discharged two years later and he has continued to make a satisfactory social and economic adjustment and is otherwise in good shape at the present time.

In 1923, other American psychiatrists took up this form of treatment and for the past years this treatment has been given continually at St. Elizabeths to all paretics as soon after admission as possible and to date we have successfully inoculated over four hundred cases.

PART I*

RESULTS OF MALARIAL INOCULATION OF PARESIS

Realizing that paresis is a disease that often assumes a slow, chronic course during which spontaneous improvement, lasting varying periods of time, often takes place and that the clinical picture shows a great diversity of changes which may be subject to various faulty interpretation, the board appointed for the study of this experiment decided to adopt a certain standard which could be utilized in measuring the amount of change, for better or worse, with as fair a degree of accuracy as possible.

It was decided to examine each patient before inoculation and at certain periodic intervals subsequent to it, and that such an examination should consider the disease from the three main levels: the neurologic, the serologic and the mental, and that the findings at each level be expressed by symbols indicating the degree of involvement present corresponding in a general way to the clinical types of early, moderately advanced, and advanced, using for such purposes the letters *A*, *B* and *C*.

Thus a patient who from a neurologic standpoint showed pupils reacting sluggishly to light, some exaggeration of deep reflexes with slight slurring in speech—observed only in special test phrases but not in general conversation—but whose coördination did not show any abnormality and the general physical examination was otherwise negative was given a neurologic rating of *A*.

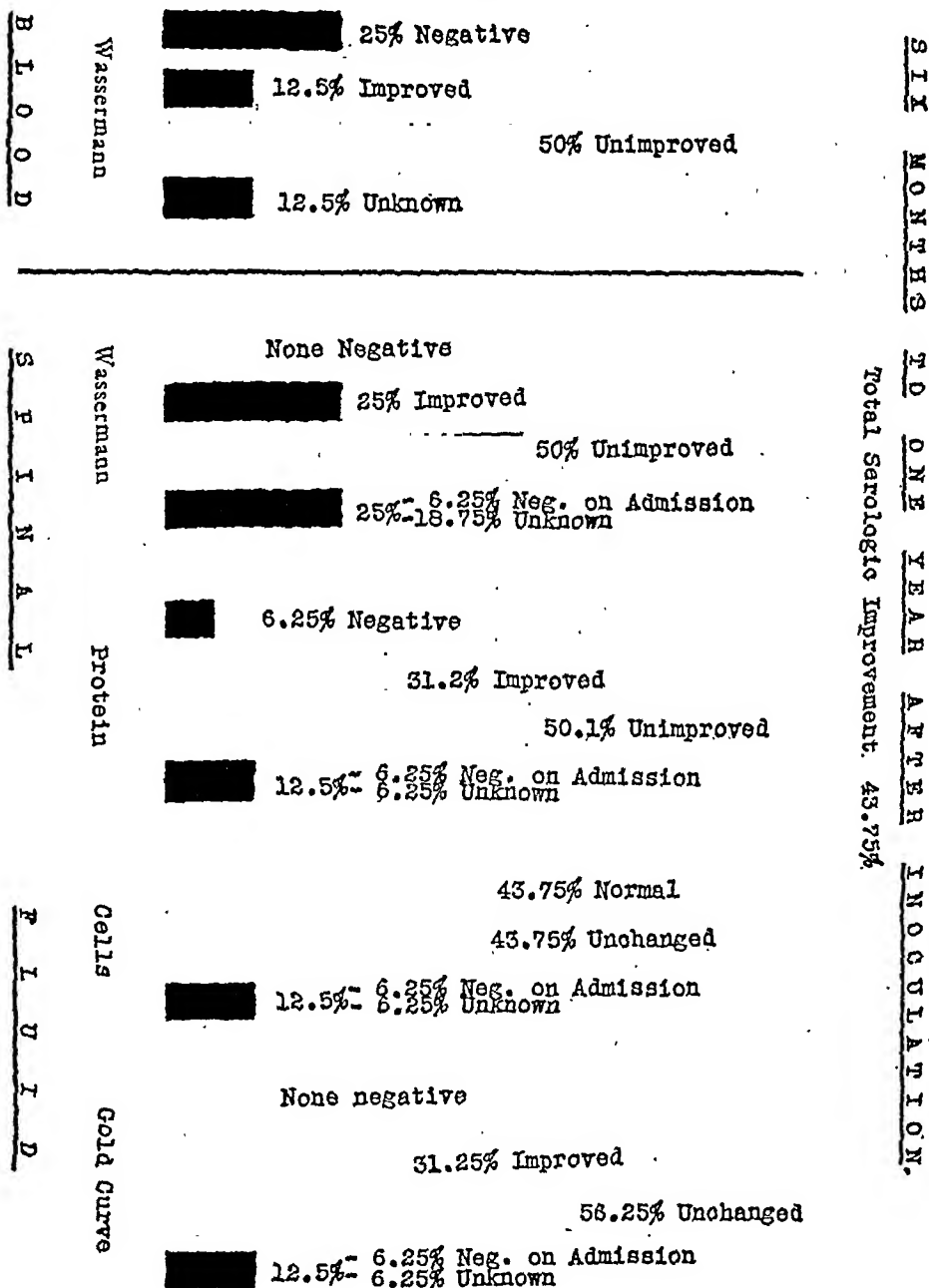
When, however, the pupils were irregular or unequal with very little or no reaction to light, facial tremors were present with some noticeable slurring of speech during ordinary conversation and with characteristic failure in test phrases, some awkwardness in station and gait, some incoördination of the upper or lower extremities with definitely exaggerated reflexes, but in good general physical state, the case was rated *B*.

Rigid pupils, characteristic speech defect, marked facial tremors, incoördination of the upper and lower extremities, impairment in gait with markedly exaggerated or absent deep reflexes with, perhaps, some loss of weight, the rating was *C*.

* Material put together and prepared by Dr. S. A. Silk.

The mental symptoms and the serologic findings were considered in a similar manner.

GRAPH 2.



For purposes of finer differentiation as to degree of involvement at each level, we used signs plus and minus; thus, A plus indicated

SPECIMEN CHART

John Doe. Case No. 37693.

Lesion.....	1911			
Admission.....	4-29-22			
Previous treatment.....	Salvarsan 6; gray oil 4.			
Inoculation.....	8-17-23			
Results.....	Ten paroxysms the tenth day; type D.T., 103.2, severe; quinine venously.			
Treatment after inoculation	None			
Survey.....	Neurologic	Serologic	Mental	
	B	C	B+	4-29-22
	B	C	B+	8-17-23
				(Inoculation)
	B-	C	B	12-20-23
	A+	B	B-	4-15-24
	A+	B	A+	8-10-24
	A	A+	A	3-10-25
Disposition.....	The patient was discharged as social recovery 3-15-25; classified markedly improved.			
Follow-up history.....	The information obtained from the patient was corroborated by friends and relatives, the report being that the patient gets along very well, successfully conducts a school of music, takes care of his family and shows no evidence of mental abnormality and is quite well physically. Above condition on June 10, 1928.			
Clinically.....	Social recovery			
This study.....	Markedly improved			

more than the average under *A*. *B* minus, not quite as advanced as *B*, but more advanced than *A* or *A* plus. *B* plus and *C* minus indicated corresponding difference so that actually seven degrees were used expressing the pathologic involvement at each level.

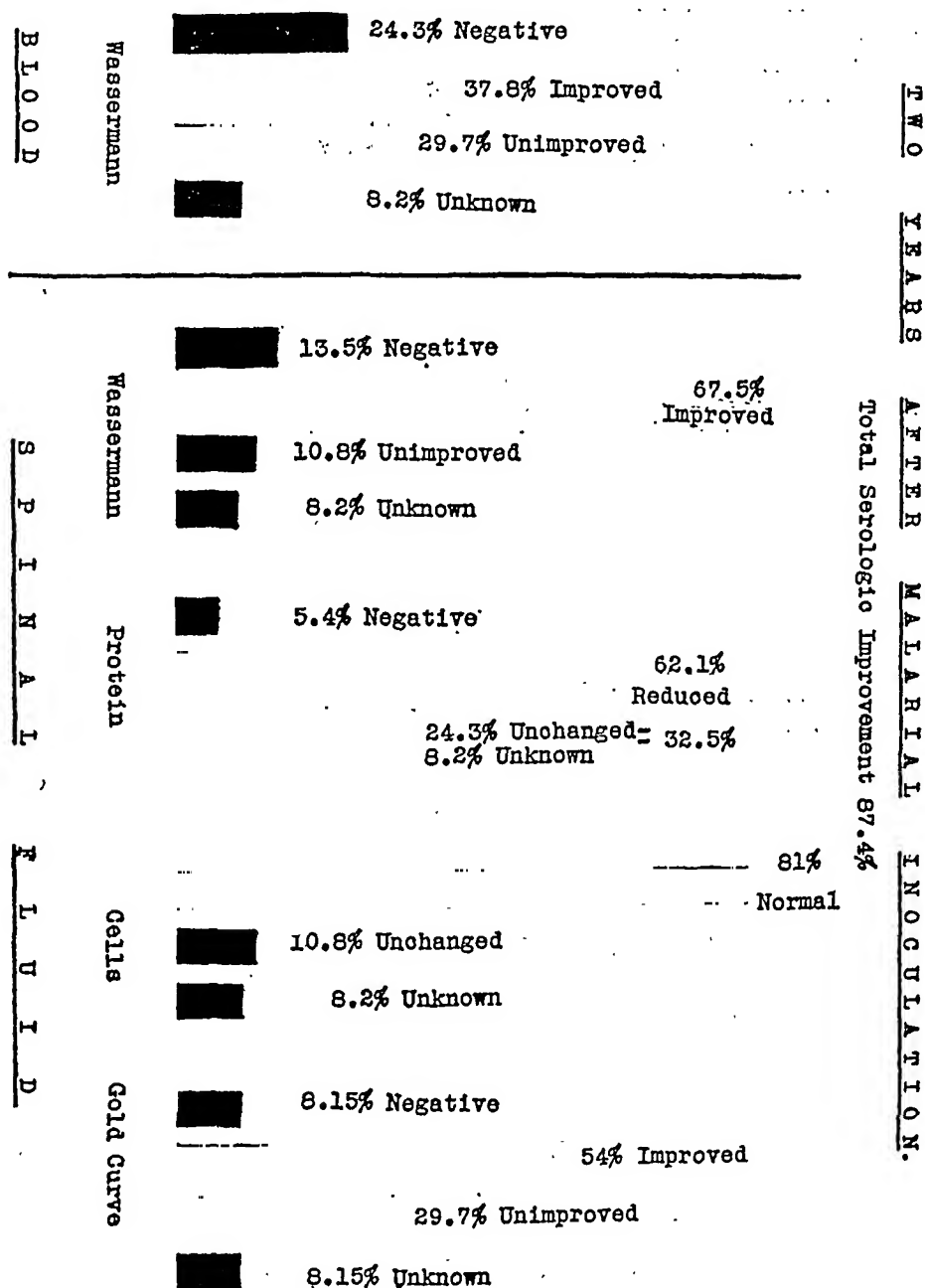
Only cases definitely diagnosed paresis by the hospital staff conference with the concurrence of the board were included in this study and in all cases the serology was typical of paresis.

The board held meetings at stated intervals, and had the services of a stenographer who then and there recorded the opinions of the members of the board with regard to the result of the examination in each case.

A chart was maintained for each patient, where was recorded the patient's name and date of admission, the kind and amount of any previous treatment received, whether patient had ever had malarial fever and other points of special interest in connection

with each patient; then followed the so-called "rating" at each level—neurologic, serologic and mental—the results of the inoculation

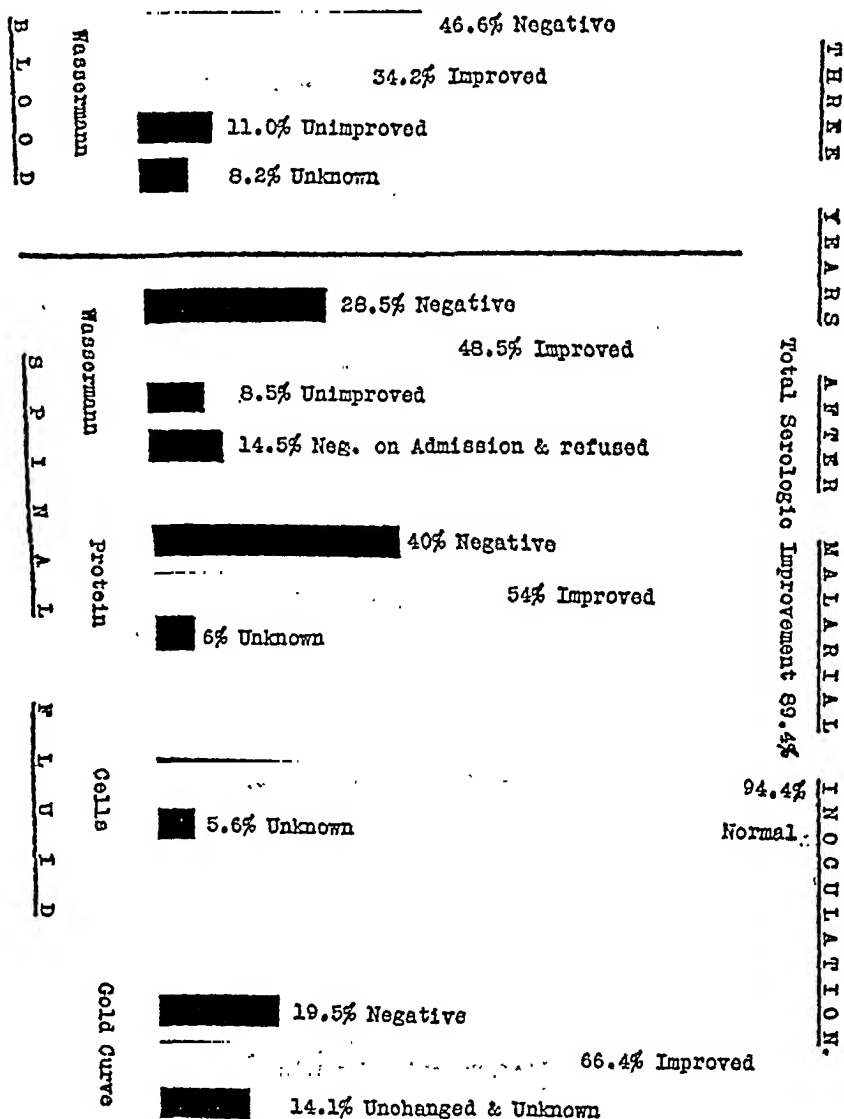
GRAPH 3.



giving number of paroxysms, period of incubation, type and height of fever, and whether quinine was given to check the paroxysms or

they ceased spontaneously, and finally dates and ratings of subsequent examinations and a general summary when the case was closed.

GRAPH 4.

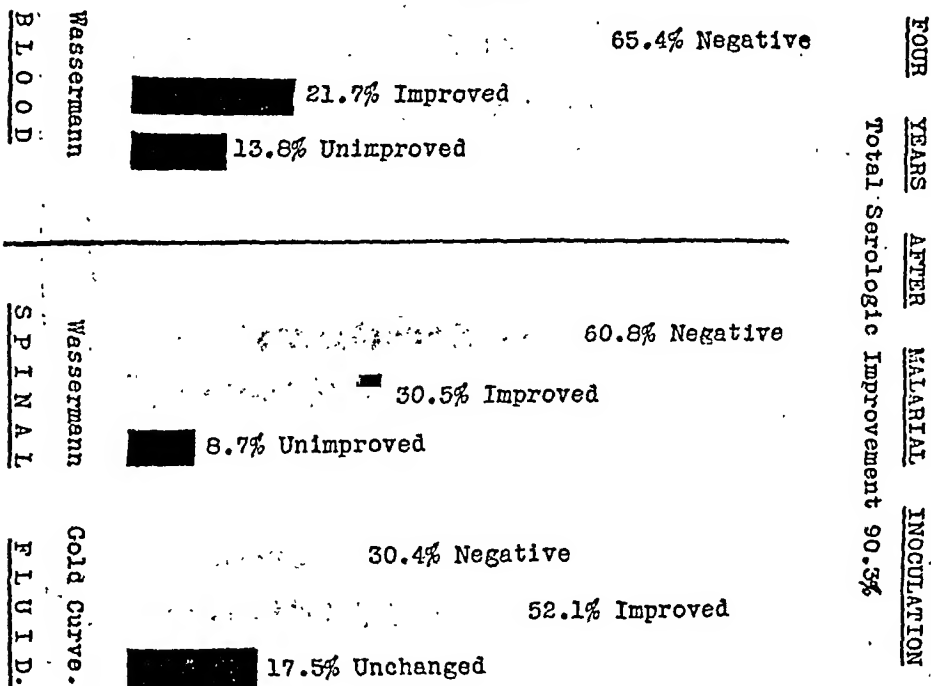


In rating our patients, at each examination we considered not only the cross section of the patient as observed at the time of the

examination but had before us his entire record describing his everyday behavior, his occupational activities and his general adaptability. Frequently the patient's physician in charge was consulted before giving the patient his rating.

The reason for going into such details as to the method of our study is because it is felt that this gives the reader an opportunity to evaluate our classifications and such designations as "improved," "marked improvement," "unchanged," and "progressive."

GRAPH 5.



Many writers on the subject in giving their results of the treatment, use the term "remission" but unless it be clearly defined and the length of time embraced by such remission specifically given, it conveys very little information as to the efficacy of the malarial treatment in a given case.

Perhaps mention should also be made of the fact that all the examinations of patients made here, were performed in the presence of all members of the board and the findings as given are the unanimous opinions of the three members comprising the board.

The results as given below are presented under the following groupings:

1. Improved—with subdivisions:
 - (a) Moderately improved
 - (b) Markedly improved
2. Unchanged
3. Progressive
4. Died

In the general group of improved, are included cases in which a definite change for the better has taken place, at each of the three levels of the disease, or if at two levels, the symptomatology at the third level remained unchanged.

A case, however, showing improvement at one or two levels, but a progressive condition of the third, is classified as progressive from the standpoint of results of the treatment.

Improvement of one degree even at all three levels is considered under the subdivision—(a) Moderately improved.

When the change for the better is two degrees in one or more levels, while one degree improved at the others or even remaining unchanged at one level, such a case is placed in the subdivision—(b) Markedly improved.

TABLE I

Results in 192 Successfully Inoculated Cases

Improved.....	140
(a) Moderate improvement, 93	
(b) Marked improvement, 47	
Unchanged.....	14
Progressive.....	20
Died.....	18

TABLE II

140 Improved Cases Studied from Each of the Three Levels of Involvement

	Unchanged	Improved		
		(a) Moderate	(b) Marked	Total
Neurologic.....	27	113	0	113
Serologic.....	48	45	47	92
Mental.....	29	89	22	111

Thus a case which upon initial examination was rated but *C—* *B+* *C—* and at a subsequent examination received the rating *A+* *A B—* would be considered markedly improved.

Serologic improvement appears much later than either neurologic or mental. Rarely is any noticeable improvement observed before the end of one year but once improvement is initiated serologically it is usually continuous and in almost 50 per cent. of the improved cases the serology becomes normal.

TABLE III
140 Improved Cases Studied from the Clinical Standpoint

Clinical Types	Number of Cases	Results	Neurologic	Serologic	Mental
Mild	22	Unchanged	5	9	9
		Moderately improved	17	5	5
		Markedly improved	0	8	8
Moderately advanced	96	Unchanged	18	30	14
		Moderately improved	78	33	66
		Markedly improved	0	33	16
Advanced	22	Unchanged	4	7	8
		Moderately improved	18	8	10
		Markedly improved	0	7	4

Percentage of Improvement

Level Studied	Mild, Per Cent.	Moderately Advanced, Per Cent.	Advanced, Per Cent.
Neurologic.....	77	81	82
Serologic.....	59	69	68
Mental.....	59	85	64

The entire group of improved cases may be considered as definitely arrested, and the cases in which the arrested condition has continued for periods of two and three, and four and even five years could with justification be regarded as cured when considered from the standpoint of the activity of the pathologic process, although not in the sense of complete structural restoration.

Neurologically the improvement in all cases is only of moderate degree.

Statistical Results of Malarial Treatment

From December, 1922, to October, 1928, 192 patients were successfully inoculated with malaria with the following results:—140 cases were definitely improved; ninety-three showing marked improvement. In fourteen cases the condition remained unchanged. In twenty cases the condition was progressive and eighteen cases died. (See Table I.)

This group of 140 improved cases was studied from a great many standpoints as may be seen from the various tables hereto appended. Table II, however, deserves special comment.

This table shows that the neurologic level was improved in the greatest number of patients.

One hundred and thirteen patients out of the 140 are marked as improved in the neurologic tests; 111 cases showed improvement in the mental grouping and of the 140 there were ninety-two listed as improved in the serologic examination.

So far as the degree of improvement is concerned, the neurologic level is the least responsive one to treatment. An advanced case at all levels may become practically normal—the serology may become normal; mentally all the symptoms may disappear, but if the neurology once reaches the advanced stage *C*, only a moderate improvement can be expected. There may be improvement in coördination, facial tremors may become less marked, speech less tremulous, the slurring less pronounced, and there may be improvement in the reflexes, but most of the symptoms will persist to an appreciable degree.

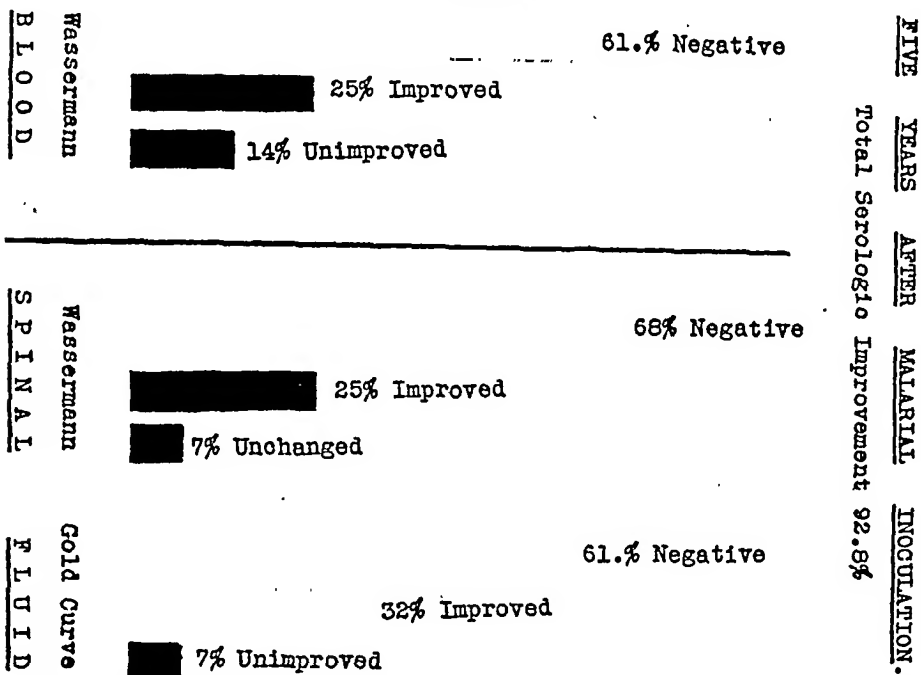
This would indicate, neurologically at least, that the earlier the case is treated, the better results may be expected.

The beneficial results of malarial therapy may be seen when we

compare the group of 192 successfully inoculated patients with a group of 214 successive admissions to the hospital. These latter did not receive malaria but did receive arsphenamin treatment.

Of this group of 214 patients, 137 patients were dead within periods less than one year after hospital admission and only five patients of this group were alive five years after their hospital admission.

GRAPH 6.



In the malarial group only eighteen cases died within a period of less than one year and most of these had been inoculated when in the advanced stage of the disease. One hundred seventy-four patients were alive five or more years after admission and of this group sixty were so improved that they were living outside the hospital and supporting themselves, forty of whom were discharged while the others continued to have nominal hospital supervision.

A survey of all the paretic patients in one of the hospital departments (Richardson Group) discloses the following interesting facts.

This Service now has fifty-five patients suffering from paresis. With one exception these have been successfully inoculated.

The average length of residence for the entire group is four years. Some have been here eight, ten, and twelve years.

Of this group of fifty-five cases, thirty-five patients have ground parole while twenty of the thirty-five have also city parole. Fifteen are on the "visit status." Thirteen patients make good ward adjustments. Some of these are candidates for parole. Seven are quite deteriorated but present no problems of care. Only two cases constitute problem cases. They are untidy and at times mildly destructive.

All the paretics in this department constitute a group of best behaved patients presenting practically no problems of management whereas patients who did not receive the malarial treatment belonged to the most troublesome group of patients in the institution.

The death rate at St. Elizabeths Hospital for a two-year period for the two classes of patients is shown below. In one class are those who did not receive malarial treatment while in the other are those patients who received the inoculation. This is a reduction in mortality of 62 per cent.

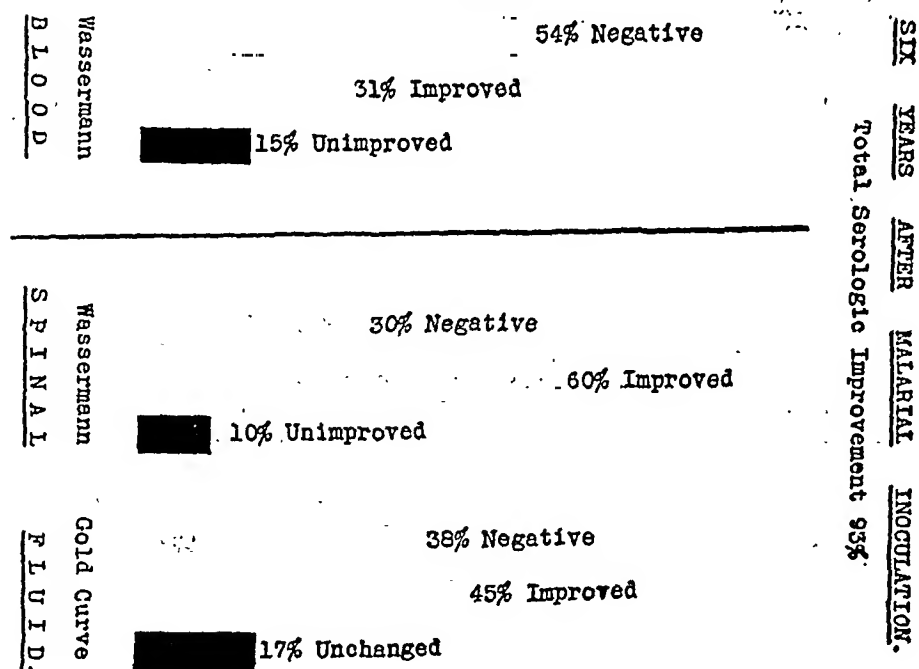
Year	Deaths from Paresis Pre-Malarial Era	Year	Deaths from Paresis Post-Malarial Era
1921.....	61	1929.....	28
1922.....	62	1930.....	19
Total.....	123	Total.....	47

When we further analyze the forty-seven patients that died from paresis during 1929 and 1930 we find that the groups consisted of twenty-one white and twenty-six colored patients. None of the colored had been successfully inoculated with malaria. (The majority of the colored patients do not react to malarial inoculation.) Of the twenty-one whites only five patients had been successfully inoculated, the others being either cases admitted to the institution in such an advanced stage of the disease that death followed shortly after their admission and before there was available malarial blood for inoculation, or in whom the inoculation did not take. We are justified in the conclusion that if the group of those who died during 1929-1930 had been successfully inoculated the reduction in mortality would have been even greater.

The most striking results of the malarial therapy are seen in the changes of the serologic reaction in the blood and spinal fluid.

The blood Wassermann is the first to show the beneficial change; this is followed by the improvement in the Wassermann of the spinal fluid. In most of the improved cases this becomes promptly negative, while in a smaller number of cases the improvement is more gradual, becoming negative in the weaker dilution and weakly positive in the stronger dilution, finally becoming completely negative. At the same time a marked improvement takes place in

GRAPH 7.



the colloidal gold reactions, and in a few cases the colloidal gold is completely negative by the time the Wassermann in the cerebrospinal fluid becomes negative. In most of the cases, however, there is a gradual reduction of the colloidal gold curve to complete normalcy. In the majority of cases marked changes in the colloidal reactions do not occur before about one year after treatment while it may take from two to three years before the gold reaction becomes normal.

A review of the serologic changes in 174 malaria-treated cases during the period 1923 to 1930 by Dr. Theodore C. C. Fong, at St. Elizabeths Hospital, gave the following interesting results.

Total Serologic Improvement.	Per Cent. Remained Unchanged	Per Cent. Undetermined
84	10.5	5.5

The accompanying graphs are especially illuminating with reference to the slow but steady, progressive, favorable changes in the serology to the point that after six or seven years; we get nearly 100 per cent. improvement in the spinal fluid, and in nearly 50 per cent. of the cases the spinal fluid is entirely negative. They also show that the serologic improvement is very gradual and it sometimes takes a year or two before improvement is noticed in the serology, although at other levels the improvement is shown very soon, so that actually we see that cases sometimes take three or four or more years before the spinal fluid becomes entirely negative. For example, in none of the cases, one year after inoculation, is the spinal fluid negative, whereas there is progressive improvement until, at the end of eight years, the result is 100 per cent. improvement and in nearly 50 per cent. of the cases the spinal fluid is completely negative. Of the various components of the spinal fluid, examination shows that the more rapid beneficial changes are observed in the protein and cell count—three years after inoculation the improvement in the protein and cell count is nearly 100 per cent. This is followed by improvement in the Wassermann and finally in the colloidal gold.

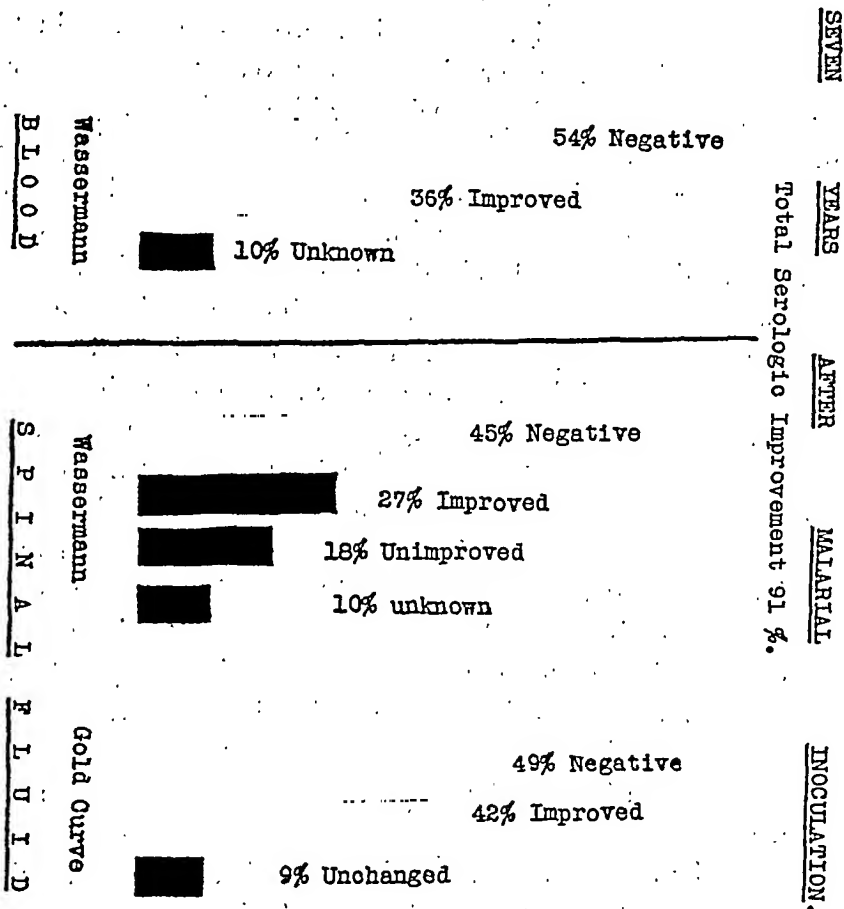
Such results were practically never observed before the introduction of the malarial treatment, although very intensive arsphenamin treatment by every known method was carried out in St. Elizabeths Hospital in a large number of cases. This has also been the experience of other syphilologists.

Fordyce* states: "Very few of our paretics become serologically negative; occasionally we can influence the Wassermann reaction in the blood. In paresis, the great majority, perhaps 99 per cent., have a very strongly positive blood and spinal fluid. In very few cases

* For bibliography see: FORDYCE, JOHN A.: "Intraspinal Treatment in Syphilis of the Central Nervous System. The Human Cerebrospinal Fluid," *Association for Research in Nervous and Mental Disease*, vol. 4, pp. 494-520, published by Paul B. Hoeber, New York, 1924.

are the findings in the fluid, other than cell count and globulin content, altered by treatment." Those who uphold the efficacy of intravenous and intraspinal treatment of paresis emphasize "adequate" and "persistent" treatment of early paresis over a period of many years until the serology is negative.

GRAPH 8.

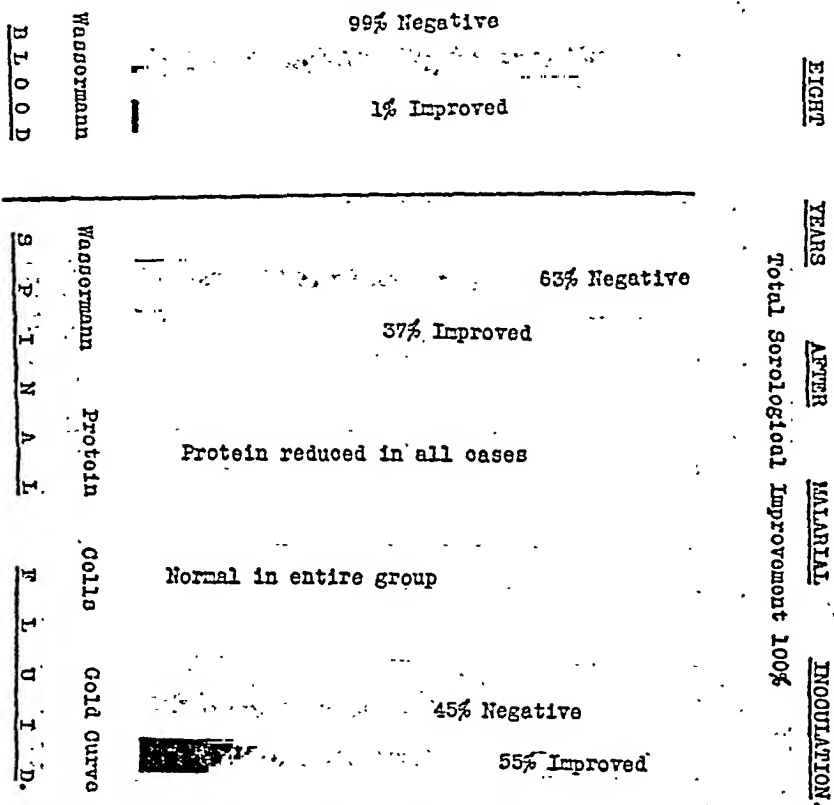


Fordyce, as quoted above, states that very few cases of paresis, in fact, ever become serologically negative, but even as a prophylactic measure against paresis the efficacy of arsphenamin may be questioned.

Before the introduction of intravenous and intraspinal arsphenamin therapy, general paresis was rarely seen in a shorter period than ten years after the initial infection, whereas, in recent years we have received in St. Elizabeths Hospital a number of cases of paresis where this disease developed two or three years after the

initial lesion, in spite of the fact that such patients received active intravenous treatment immediately following the infection and the treatment was continued until serology became negative. This was observed in many of the cases coming from the Army and Navy with records giving the exact date of the observance of the initial lesion, the number of arsphenamin injections administered until the

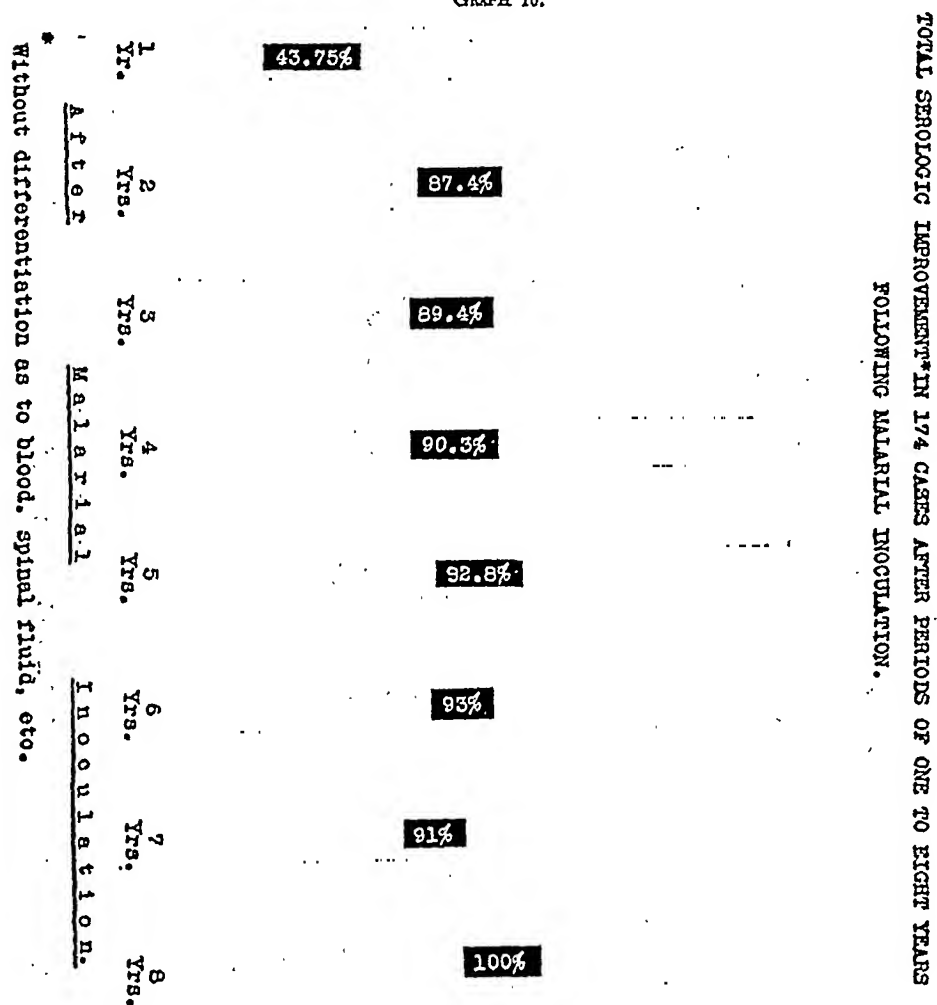
GRAPH 9.



Wassermann became negative. It should be stated, however, that in the majority of such cases the spinal fluid was not examined and the treatment was discontinued when the blood Wassermann became negative. In this connection a comparison of cases of paresis admitted from the military establishments with those from the civilian population of the District of Columbia would further tend to confirm the adverse opinions concerning the efficacy of arsphenamin therapy as a prophylaxis against paresis, as compared with the old time mercurial treatment.

In the great majority of the paretics from civilian life, paresis developed fifteen to twenty years after the initial infection, although treatment was carried out only for a brief period consisting of some mercurial rubs and protoiodide tablets internally until secondaries disappeared; rarely was treatment continued longer than one year.

GRAPH 10.



Cases coming from the military establishments—would show paresis after a period of from five to ten years; many as stated above, two or three years after the initial lesion, although such cases were from the very beginning under constant care of competent medical officers of the Army or Navy and received intensive arsphenamin treatment.

(To be continued.)

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